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THE MONTH

THIRTY years ago the cardiologist's pharmacopœia consisted of two drugs—digitalis and trinitrin—and a very good pair of drugs they were. Today his pharmacopœia has extended out of all recognition. Some of these additions are valuable, others are little more than placeboes, whilst a few do more harm than good. Of proven value are the antibiotics, which have revolutionized the outlook in subacute bacterial endocarditis and are of value in the prevention of rheumatic heart disease, and the new oral diuretics. Of more limited value are the hypotensive drugs, whilst the experts are still disputing the value of the anticoagulants. If patients are to obtain the full benefit of these new preparations, it is essential that the practitioner should be able to use them with discrimination, and it is as a guide to him in this task that we have devoted the symposium in this Special Number to 'Cardiovascular therapy'. Pride of place is rightly given to digitalis, because it is still the most useful drug in the treatment of heart failure, and it is only fitting that this introductory article should come from the Cardiac Department of the London Hospital, the founder of which was Sir James Mackenzie, who did more than anyone else to put the use of digitalis on a rational basis. It will also be noted that, in spite of the vasodilator drugs now on the market, none has equalled that of trinitrin in the treatment of angina pectoris.

The Symposium

THE present Government's record on the subject of private patients obtaining their prescribed drugs through the National Health Service is a particularly unpleasant example of political sophistry. In 1949, as the political correspondent of *The Times* has recently pointed out (November 28, 1960), 'in "The Right Road for Britain", and again in "Conservative Policy", the Conservatives pledged themselves that "we shall allow private patients to obtain free of charge drugs prescribed by their doctors on a parity with people in the state scheme". Ever since then successive Conservative Ministers of Health, like Mr. Enoch Powell, have declared that there is nothing contrary to Conservative principles in the supply of drugs to private patients in the Health Service'.

Drugs for Private Patients

Why is it then that this pledge has never been fulfilled? In 1951, financial stringency was the excuse. When the nation weathered this period, the

excuse was that the granting of this 'concession' would be abused by doctors. When reassurances were obtained about this, with the acceptance by the profession of corresponding safeguards, the excuse was that the 'concession' could only be granted if there were evidence that the withholding of it would prejudice private practice. The resilience of private practice is such that this last excuse is as unanswerable as it is irrelevant. Is it possible that the Government shares the view of *The Economist* (December 3, 1960) that there is 'a much stronger case for restricting the health service facilities that a doctor's private patient can use rather than for extending them by allowing him health service drugs. An extension could provoke an undesirable division—first class for private patients, slightly more utility class for public patients—in the standards of general practice'? The sad tale of the last decade certainly suggests that the ultimate aim of the present Government is to do all it can to rid the country of private practice. If this is the aim, then honesty insists that they should say so. If this is not their aim, then honesty equally insists that they should accept the motion now tabled in the names of over a hundred Conservative back-benchers, and enact forthwith the necessary legislation to allow private patients to obtain their drugs through the National Health Service—not as a concession, but as a right.

B.U.P.A.

It was with justifiable pride that at the recent annual meeting of the British United Provident Association (B.U.P.A.), the Chairman, Sir Andrew Rowell, was able to announce that the Association had now a registered membership of over 800,000. So far as can be made out, this means that nine out of every ten members of provident associations in this country belong to B.U.P.A. That members are getting value for money is clear from the fact that of the £3½ million received as subscriptions in the financial year ended June 30, 1960, £3 million was paid out to members by way of claims and outstanding provisions, and only £300,000 went in expenses. This is in keeping with the aim of the board of governors—to distribute 85 per cent. of income in claims, and keep the expense ratio to 10 per cent., leaving a balance of 5 per cent. to put to reserve. As the Association met no fewer than 100,000 claims in the year under review, this low expense ratio is indeed commendable and, as the Association's reserves now approach £1 million, members have every reason to be satisfied with the service they are receiving.

Through the Nuffield Nursing Homes Trust, the Association is steadily expanding its efforts to meet the current acute shortage of nursing homes. The existing homes at Bournemouth and Harrogate are operating satisfactorily. Alterations and modernization are being carried out to existing homes at Bath and Edinburgh, an extension is being made to the Harrogate home, and new homes are being built at Exeter and Woking. The most

ambitious project of all is the nursing home which the Trust is hoping to build on a site it already owns in Bryanston Square in London. As things are developing at the moment it looks as if by the end of 1961 the Trust will be owning and administering ten nursing homes. This progress report will be of particular interest to our readers who are members of *The Practitioner* B.U.P.A. Group. Those of our readers in Great Britain and Northern Ireland, who are not already members of this Group, are reminded that by joining the Group they can register with B.U.P.A. for sickness benefit at a reduction of 20 per cent. in the standard premium.

Principles of Rehabilitation

In this gadget-minded age there is a real danger of the 'experts' in our midst adding yet another hazard to the life of the crippled and the disabled—learning how to work the gadgets. What is tending to be forgotten is that the whole object of rehabilitation is to provide the patient with a life as near normal as possible by helping him (or her) to obtain the maximum of independence. Unnecessary dependence on gadgets is just as reprehensible as unnecessary dependence on others—whether they be relatives, neighbours, nurses, or health visitors. Not only are many of these gadgets, or aids, unnecessary, they are often unnecessarily complicated and expensive.

Amidst all this welter of 'gadgetry', first principles are being forgotten, and it is for this reason that we are proposing to publish a series of articles on 'Principles of Rehabilitation'. Written by the director of one of the most progressive departments of physical medicine in the country, their aim is 'by discussing the principles involved' to make it 'easier for the family doctor to select the aid most suitable for the individual patient'. The first of the series—on 'Walking Aids' (p. 135)—illustrates admirably the author's approach to the subject. Throughout the whole series it will be found that the emphasis is on the independence of the patient and how in many cases this can be obtained with the expenditure of a little care, forethought and encouragement.

WHO News

We in this country tend to accept the World Health Organization as a fact—and not necessarily a particularly interesting one. It seems to have so little to do with our day-to-day work. To our opposite numbers abroad, however—particularly in Africa and Asia—it is one of the most important organizations in the world, with a record in the field of malaria and yaws eradication, for example, that stands unsurpassed in the history of medicine. What we in this country have to realize is that in the world as it exists today the health of the nation is almost equally dependent on the work of WHO. Of equal import is the fact that we have a duty to ensure that Britain plays an active part in the work of the Organization.

To ensure this aim of full participation, knowledge is necessary, and it is for this reason that this month we are introducing a new feature in *The Practitioner* in 'World Health News: A WHO News Bulletin'. The aim of this new feature, the first instalment of which is published on p. A 15, is to provide a monthly summary of the more important developments in the work of the Organization. This, it is hoped, will prove of interest to our readers both at home and abroad, and allow them to keep up to date with the whole field of international medicine covered by the activities of WHO.

Arsenic, Cigarettes and Lung Cancer

'It is depressing to contemplate present-day inertia in the smoking-cancer problem, frustrated in a tangle of controversy and mixed motivation, without prospect of the authoritative organization and coordination of action that its solution demands'. So writes Henry S. Satterlee (*New Engl. J. Med.*, 1960, **263**, 676) in a stimulating, if provocative, review of the part played by arsenic in the causation of cancer of the lung. In contrast, he draws attention to the efficient manner in which the 1900 episode of arsenic poisoning in Lancashire, due to contaminated beer, was handled by the appointment of an authoritative Royal Commission under the chairmanship of Lord Kelvin. Although the major cause of the outbreak was arsenic-contaminated glucose, Satterlee draws attention to the finding of the Royal Commission that another source of arsenic contamination was 'the regular practice of drying the malted barley . . . in the fumes of arsenic-containing malting fuels'. This, as he points out, is a 'feature that may have application today in the flue-curing of tobacco'. He further notes that in 1923 American cigarettes contained seven to ten times more arsenic than those made from imported oriental tobacco, and by 1951 this ratio had increased to about 40:1.

Although the whole history of cancer research has been bedevilled by partisanship for some pet theory, there can be no question about the importance of arsenic as a carcinogenic agent. What is probably not realized, however, is the extent to which the atmosphere and the population are contaminated in this way. Satterlee, for instance, quotes figures showing that the average arsenic concentration in expired air—110 micrograms per cubic metre—is nearly three times the tolerance limit set for 'background arsenic' under controlled conditions in a microanalytical laboratory. 'What' therefore he asks, 'may be the arsenic content of the confined atmosphere in crowded vehicles and in places of assembly such as omnibuses and subway trains during rush hours, and in cinema theatres?' Opinion may be divided as to the advisability of appointing a Royal Commission on the problem of cigarettes and cancer of the lung, but there would seem to be a strong case for a further investigation of the part played by arsenic in this complex problem.

DIGITALIS THERAPY

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To write about a hypotensive drug, alleged to be capable of subduing the blood pressure and allaying the symptoms of hypertension, is to write cautiously, lest its apparent initial success should recede during its continued usage, and bring it to rest in the archives of forgotten remedies. To write about digitalis, however, is to write about a physician's tried and trusted ally. Its lustre as the heart's breastplate has not dimmed through well-nigh two centuries of time. Nothing therefore needs to be said in its favour because nothing can be said against it. Certainly, we should never decry a medicine which has so proved its worth.

Nonetheless, the principles that govern digitalis therapy are not always honoured, and there is still a tendency to be unmindful of the special circumstances presented by individual patients who differ from one another in regard to the extent of their need of the medicine, and in their response to it.

WHAT IT DOES AND IN WHAT MANNER

The effects of digitalis on a patient with heart failure are plain to see, and they are readily observed at the bedside. The patient will have noticed many of them, the nurse in attendance will have recorded most of them, and the visiting physician will have found no difficulty in confirming all of them, and without the aid of elaborate laboratory tests. Thus, breathlessness diminishes, peripheral œdema, should it be present, recedes, venous pressure is lowered, the heart rate slows, the heart size diminishes somewhat as does pulmonary congestion, diuresis takes place, and the body weight falls.

The precise mechanism by which these desirable effects are brought about continues to evade experimentalists who in their turn have stressed their individual beliefs as to what happens. These include a vagal effect which slows the heart rate, constriction of hepatic veins which reduces the venous pressure, some vague action on the peripheral vasculature, diminished water content and readjusted electrolytic balance within the heart muscle following diuresis, and a *tonic* action on the muscle fibres which diminishes the size of the heart, increasing its power of contraction and its output during each heart beat, so that the circulating blood moves at a higher velocity, relieving ischæmia in the viscera ahead.

While this uncertainty lasts about the precise way in which digitalis brings benefit to the failing heart, I draw comfort from the definition of its action given by a Nursing Sister to her class: 'It slows the heart, lengthens the pause, enabling the heart to gain nourishment from its own improved circulation'. After all, the involved details of the exact mechanism of any change, either in movement or form, should not make us despondent because of our inability to explain it, or drive us into the wilderness of exhaustive

investigation at the expense of clouding our minds to the realities that matter: namely in this context to acknowledge the sterling worth of digitalis in many, and its real succour in most, instances of heart failure, and to apply it intelligently in the separate circumstances in which the patients present themselves for treatment.

PREPARATIONS AND DOSAGE

As with all effective medicines it is natural for digitalis to be marketed in different forms. Thus, in addition to its infusion and tincture which were formerly used, there are digitoxin, digitalin, lanatoside C, gitalin, digoxin, and the official preparation of the leaf. The choice should be made on the grounds of effectiveness and cheapness. Naturally, the proprietary preparations are more expensive, and a further disadvantage is the variation in their potency, so that although the separate brands may be supplied in the same bulk dosage, the quantity of the active principle that each harbours may differ considerably, and this is well exemplified in the case of many brands of digitalin for instance. Having these difficulties in mind, the leaf has proved the best for continuous use. Should any physician prefer another kind he will inevitably have based his choice on his own experience or on the advice of his elders, and not on the persuasive blandishments of a highly geared salesmanship which is now identified with proprietary establishments.

Preparations having a like action to digitalis, such as strophanthin, folinerin and ouabain, are no match for digitalis, and they can stake no claim to further comparative clinical trials.

By *digitalization* is meant that amount of digitalis which is sufficient on the one hand to keep the patient free from the symptoms of heart failure, and on the other hand not in excess so as to cause toxic effects. In that digitalis is cumulative, its continuous administration is conveniently effected through adherence to a constant single dose, e.g. one grain (60 mg.) of the leaf as prepared digitalis tablets B.P., and varying the daily dosage, dispensing it twice daily, or twice and once on alternate days, according to the patient's need. It is inexpedient and unwise to estimate this need by recourse to set formulæ like Eggleston's which calculates the surface area of the body and its weight. A big dose for a big man is never sound reasoning in regard to digitalis dispensing, for the size of the heart as well as the size of the body has to be reckoned with, whilst the heart's appetite for digitalis in a given patient can never be predicted, so that a decision on the proper dosage has to be made following a clinical trial.

During such a trial a common fallacy is to nominate a ventricular rate of about 70 beats a minute as standard in fibrillation and as an index that the point of adequate digitalization has been reached. It should be known that, whilst such a rate may be ideal for the majority, in some it may be 90 and in others it may be as slow as 55 a minute. It is a rare need for digitalization to be instituted speedily, and even when the heart rate exceeds 150 a minute there can seldom be any desperate hurry to slow it. If, however, a decision

has been taken to apply *rapid digitalization*, it is best ensured by digoxin: 2 mg. by mouth or 1 mg. intravenously; the former route is as effective as the latter, and the heart rate is satisfactorily subdued in less than an hour.

TOXICITY

The toxic effects of digitalis have received too much attention in the past for they have too often meant a denial of its benefit to patients in need of it. After all, most medicines produce untoward effects if given in unreasonable and excessive doses. It is necessary to realize that gastro-intestinal symptoms, such as anorexia, nausea and vomiting, are common symptoms in patients with heart failure, and that these are more likely to abate from doubling rather than halving the amount of digitalis. The addition of extrasystoles, which in the presence of fibrillation may cause coupling of the pulse, should never be regarded by itself as a signal to withdraw digitalis therapy from a patient otherwise benefiting from its action, for many show a natural liability to develop this rather innocent arrhythmia.

The depletion of potassium through the repetitive use of diuretic drugs may induce atrial tachycardia with varying A-V dissociation, and this arrhythmia should not be attributed solely to coincident digitalis therapy.

INDICATIONS

'Once digitalis, always digitalis' is a wise practical precept and applies in most circumstances, except of course when prescribed where there was no call for it, and when therefore no good was expected from its use. Digitalis does not produce the same beneficial effects in every clinical state in which heart failure has been added, and some of the circumstances which decide its success are known; these are related to the cause of the heart failure, to the side of the heart mostly or solely under duress, to the heart rate, and to the presence of arrhythmia. When the heart rate is rapid and regular (sinus tachycardia) the rate is more likely to be reduced by digitalis if heart failure is also present, and this is exemplified by many but not all cases of hypertensive failure. Nonetheless, in heart failure with normal rhythm the response to digitalization is rather better when the rate is slow than rapid.

Digitalization is expected to yield more favourable results in left ventricular failure than in biventricular failure where systemic congestion is added, and it is least efficacious in patients with biventricular failure and tachycardia, when it does not seem to matter whether such tachycardia is of sinus origin or appears in the form of atrial fibrillation.

Although these generalizations prove helpful in predicting the benefit which might come about from the use of digitalis, they do not invariably apply, and judgment is best founded on a consideration of the particular clinical condition which has caused the heart failure; better still is the opinion formed when examining individual patients.

VALVULAR DISEASE OF THE HEART

Mitral valve disease.—Digitalis works best of all in mitral stenosis and atrial fibrillation. It quickly reduces the rapid heart rate and annuls the pulse

deficit, while a sense of well-being is restored through the allaying of breathlessness and the ability to do more.

In *mitral stenosis* and normal rhythm where the heart is not obviously enlarged, and in the absence of pulmonary congestion, digitalization is contraindicated on the grounds that it is not needed. In the same circumstances when breathlessness is present as a result of pulmonary congestion, even though pulmonary hypertension may also be a feature, digitalis should be prescribed, but without the expectancy that it will do much good in that, short of relieving the obstruction at the valve by surgery, medication in this state fails to relieve symptoms. Certainly, when surgical treatment is planned, digitalis should be introduced beforehand and, since fibrillation commonly ensues, the medicine should be continued, for slow fibrillation on constant digitalization is more satisfactory than sinus rhythm restored and maintained by quinidine.

In *pure mitral regurgitation* when heart failure appears, it is proper to prescribe digitalis continuously, with great initial benefit, but as the left ventricle deteriorates, response to any form of medication eventually fails.

Aortic valve disease.—Before the onset of pulmonary congestion heralding heart failure, digitalis has no place in the treatment of either aortic stenosis or aortic regurgitation. When failure sets in, as a rule with normal heart rhythm, digitalization should be instituted and maintained throughout the illness, but its measure of success is small, for when heart failure makes its appearance in aortic valve disease, neither digitalis nor surgical relief of the obstruction at the valve can restore to the surrendering hypertrophied left ventricle its erstwhile contractile power.

HYPERTENSIVE HEART FAILURE

From the time of James Mackenzie onwards a debate has raged on the benefit that a patient with heart failure might expect from digitalization when the rhythm is normal. Foremost in value among the contributions made to this subject has been the work of John Parkinson (Parkinson and Clark-Kennedy, 1926; Gavey and Parkinson, 1939). Although digitalis benefits patients in abnormal heart rhythm more than those with normal rhythm, the response is likely to depend more upon the nature of the heart disease and on the side of the heart bearing the greater burden. In the left ventricular failure of hypertension digitalis will bring benefit whether in the absence or presence of fibrillation, whilst in the case of normal rhythm a reduction in rate does not ensure clinical improvement although it sometimes appears to be an advantage.

As in other instances of heart failure, so especially here, the addition of a mercurial, or other form of, diuretic is a necessity, and indeed in hypertensive heart failure digitalization is the handmaiden of whatever diuretic agent is being used. It is opportune to stress here that continued diuresis by any drug, involving the mobilization of potassium salts, will in time necessitate a reduction, or even temporary withdrawal, of digitalis.

CARDIAC INFARCTION AND CARDIOMYOPATHY

Here, too, digitalization is a need and is expected to bring benefit, and it should never be withheld on the false premise that it might induce ventricular fibrillation; if such a malignant form of arrhythmia ensues, it is the outcome of extensive destruction of the ventricular musculature, and no blame should be laid on digitalis which in these circumstances has no power to improve the heart's yielding action. Should heart failure be precipitated in hypertension by the onset of cardiac infarction, it is not uncommon experience to find that digitalis can be withdrawn after a period when it has wrought, or coincided with, distinct clinical improvement.

In the instances of so-called cardiomyopathy, it is understood that the benefit conferred by digitalization cannot be long-lived in that the progressive enlargement of the heart from dilatation following gross hypertrophy, is proof that the muscle fibres have yielded to a burden from which they cannot recover even with the aid of this its specific stimulant.

PULMONARY HYPERTENSION AND CONSTRICTIVE PERICARDITIS

Pulmonary hypertension.—When pulmonary hypertension appears by itself, or in concert with congenital cardiac shunts, mitral stenosis, emphysema or pulmonary embolism, the right heart fails in normal rhythm. Digitalis in this circumstance should never be withheld, but should never be given in anticipation that it will bring lasting or much temporary benefit, because this does not happen.

Constrictive pericarditis.—One-third of all cases of constrictive pericarditis develop atrial fibrillation, and the incidence is naturally higher in older subjects. In that the ventricular rate is moderately raised and usually to 100 or more beats a minute, digitalis is expected to produce its customary beneficial effect, but no improvement takes place from its use in the presence of sinus heart rhythm.

THYROGENIC HEART FAILURE

In thyroid toxæmia with its customary tachycardia, digitalis does not reduce the rate as effectively as iodine or antithyroid drugs. In any case, digitalization is not a method of treatment unless heart failure has been added. When failure does take place, it is in company with atrial fibrillation, when digitalis should be used temporarily and until the cause has been removed through extirpation of the over-active gland.

When removal of the thyroid, followed by full doses of quinidine, has failed to restore normal rhythm in thyrogenic fibrillation, digitalis will effectively slow the rate sufficiently to ensure freedom from palpitation during increased physical exercise which would otherwise quicken the heart rate and induce the symptom.

THE ARRHYTHMIAS

The use of digitalis in atrial fibrillation associated with most cardiac states has already been considered, and it is only necessary to mention that it is

given in *lone fibrillation* with the object of preventing palpitation during episodes of physical exertion, as in the case of postoperative thyrogenic fibrillation.

In *atrial tachycardia* with only a moderate rise in the ventricular rate (atrial flutter), continuous digitalization is effective treatment, either in the presence or absence of heart failure signs. When the ventricular rate is higher (paroxysmal tachycardia), quinidine in an attempt to annul the arrhythmia is the therapy first to adopt in the presence of heart failure, for in this circumstance digitalis will not exert its customary benefit until the tachycardia has ceased.

An excessive intake of digitalis can produce *heart block*, but should this result from myocardial disease which at the same time has induced heart failure, the introduction of adequate digitalization will convey to the patient its customary benefit and without accentuating the conduction defect. Even when Stokes-Adams disease is present, digitalization causes clinical improvement without increasing the number of the attacks. Thus, when either partial or complete heart block is associated with heart failure, usually in the company of considerable cardiac enlargement, clinical improvement, and especially the lessening of breathlessness which follows digitalis therapy, can be most rewarding.

EFFECTS ON THE ELECTROCARDIOGRAM

In these days when electrocardiography is so essential in the investigation of a patient who suffers from chest pain, the deformity in the tracing occasioned by digitalis should be known, especially when no allusion has been made to such medication by either patient or family doctor.

Although lesser changes, such as shortening of the Q-T period, and lowering of the T wave, appear after ingestion of 15 to 30 grains (1 to 2 g.) of digitalis leaf taken daily over a period of a fortnight, they are of no great moment in practice in that they are only discovered when two tracings, the one before treatment starts and the other subsequent to it, are available for comparison. The more significant changes, which are those that can be detected from inspection of a single electrocardiogram, do not usually appear until such treatment is continued for six weeks. In practice, when depression of the S-T segment is present in the electrocardiogram of a patient subject to chest pain and receiving digitalis medication, and in whom valvular and hypertensive heart disease are absent, it may be assumed that the electrocardiographic fault is the result of a myocardial injury, provided the orthodox dosage of digitalis has not been given for over a month, or provided treatment has been discontinued for a similar period.

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QUINIDINE

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THE action of the alkaloids of cinchona bark in suppressing cardiac arrhythmias was discovered by chance when a malarial patient found that his paroxysms of atrial fibrillation stopped when he was taking quinine. Subsequently it was found that quinidine was more effective than quinine for this purpose and since then quinidine has been used extensively in the prevention and treatment of disturbances of rhythm of the heart. Although potentially a toxic drug which can cause serious side-effects, quinidine if properly used has an important place in the management of the cardiac arrhythmias.

MODE OF ACTION

The action of quinidine on the heart is basically depressant, both to heart muscle and to the specialized conducting system of the heart, and the effect of the drug is sometimes difficult to predict as one or other of its actions may predominate. It increases the refractory period of heart muscle and slows conduction so that the excitability of heart muscle is decreased. It also has a direct effect on myocardial irritability and may abolish or depress ectopic foci in both atria and ventricles. In some cases the action of the vagus is depressed and a rise in heart rate is not uncommon during quinidine therapy (Gold, 1950). If given by mouth there is very little effect on cardiac output or blood pressure but if given intravenously there may be a marked fall in blood pressure due to peripheral vasodilatation.

TOXIC EFFECTS

The individual response to quinidine varies greatly from patient to patient and a distinction should be made between those toxic effects due to individual idiosyncrasy to the drug and those due to an exaggeration of the physiological action of the drug. Idiosyncrasy to quinidine is shown by the occurrence of fever, nausea, vomiting, urticaria or purpuric skin eruptions after small doses, and sometimes transient syncope or dizziness due to hypotension may occur. Very rarely sudden death due to cardiac arrest or ventricular fibrillation has followed the administration of even a small dose of quinidine. With high quinidine dosage symptoms of cinchonism are not uncommon, with gastro-intestinal symptoms of nausea, vomiting and diarrhœa, blurring of vision, tinnitus, deafness, giddiness and tremor. These effects rapidly disappear when the drug is discontinued or the dose decreased. With the usual therapeutic dosage, toxic effects of quinidine on the heart are unusual but with high dosage or following intravenous therapy there may be marked impairment of atrio-ventricular conduction

causing heart block or depression of ventricular conduction, shown on the electrocardiogram by progressive prolongation of the QRS interval. It is essential in these circumstances to control therapy with frequent electrocardiograms as these changes may be a precursor of ventricular tachycardia, fibrillation or arrest.

METHOD OF ADMINISTRATION

After a single oral dose quinidine is rapidly absorbed if the stomach is empty and the peak concentration in the blood is reached in two to four hours. Elimination is less rapid, about three-quarters of the drug being destroyed by the body and the remainder excreted in the urine, so that after twenty-four hours the quinidine level may still be as high as 10 to 20 per cent. of the peak level. With repeated dosage, such as is used for the prevention of arrhythmias, cumulation of the drug in the blood occurs over a period of four to five days and a fairly stable concentration over the whole twenty-four hours can be achieved with thrice-daily administration. In the treatment of arrhythmias quinidine is usually given at two-hourly intervals and much higher blood levels can be achieved. There is a wide individual variation in the response to quinidine, both as regards rate of absorption and elimination, and although it is known that most therapeutic successes are achieved if a level of quinidine in the serum of 0.7 mg. per 100 ml. is achieved (Sokolow, 1951) it is not practicable to control treatment with fluorometric estimation of quinidine blood levels and dosage has to be judged empirically.

Quinidine is prescribed in the form of quinidine sulphate tablets B.P. Two sizes of these are available: 3 grains (200 mg.) and 5 grains (300 mg.). Although individual idiosyncrasy is uncommon it is always wise to give an initial test-dose of 3 grains (200 mg.) before continuing treatment.

INDICATIONS

The only indication for the use of quinidine in cardiovascular diseases is for the prevention or treatment of disturbances of the normal cardiac rhythm and it has no effect on sinus tachycardia. Any improvement in cardiac function which follows its use is secondary to the slowing of the heart following restoration of normal rhythm.

ECTOPIC BEATS

These occur very commonly in both healthy and diseased hearts and in the majority of cases the patient is unaware of their presence. With the exception of ectopic beats following cardiac infarction, treatment should only be given if the patient is acutely aware of the disorderly action of the heart and if sleep is disturbed by the arrhythmia. Removal of a cause such as excessive smoking may sometimes be possible and a mild sedative such as amylobarbitone, ½ grain (30 mg.) three times a day, combined with a hypnotic at night, may

be all that is necessary in the first instance. If the ectopic beats continue to worry the patient, quinidine sulphate, 200 mg. three times a day, should be given and the dose increased at weekly intervals if necessary up to 400 mg. three times a day. The minimal effective dosage should be maintained for a period of one month and then the effects of gradually reducing it should be observed. If the ectopic beats recur maintenance therapy with quinidine can, if necessary, be continued indefinitely. Ectopic beats arising soon after a cardiac infarction may be the precursor of a more serious ventricular tachycardia or ventricular fibrillation and if they occur frequently or in short runs an attempt should be made to stop them. It is usual to try the effect of procainamide (250 mg. three times a day) in the first instance and if this fails quinidine should be given (300 mg. twice or three times a day).

PAROXYSMAL TACHYCARDIA

Supraventricular paroxysmal tachycardia.—The commonest variety of paroxysmal tachycardia is a supraventricular one occurring in a patient with a normal heart. Quinidine is the best drug for the prevention of attacks or to decrease their frequency and may be continued indefinitely: an initial dose of 3 grains (200 mg.), increasing if necessary to 6 grains (400 mg.) three times a day. In adults, if an attack fails to stop after mechanical tricks such as breath-holding, change in posture or carotid sinus pressure, or if sedation with quinalbarbitone has been ineffective, quinidine should be tried, giving 5 grains (300 mg.) two-hourly until the attack stops or up to a maximum of six doses. Children often tolerate large doses of quinidine poorly and digitalis is preferable if active treatment of the attack is indicated. Similarly in adults if attacks recur frequently, and if they precipitate heart failure in patients with heart disease, quinidine should be replaced by digitalis both for maintenance treatment and the treatment of the attack itself.

Ventricular paroxysmal tachycardia.—Over 80 per cent. of attacks of paroxysmal ventricular tachycardia occur in patients with serious heart disease and the rapid ventricular rate often causes heart failure or ischæmic pain, so that it is imperative to stop the attack as soon as possible. In cases of extreme urgency intravenous procainamide hydrochloride is safer than quinidine but, if it is decided to use intravenous quinidine, 5 grains (300 mg.) dissolved in 20 ml. of water should be injected slowly, a continuous watch being kept on the blood pressure and the electrocardiogram during administration, and the injection stopped if a marked fall in blood pressure occurs or if great widening or distortion of the QRS complex is recorded. In cases of less urgency oral quinidine two-hourly as described for supraventricular tachycardia may be tried to stop the attack and quinidine is often effective in the prevention of attacks.

ATRIAL FIBRILLATION

Paroxysmal atrial fibrillation is most commonly caused by hyperthyroidism

or rheumatic or ischæmic heart disease; less than one-sixth of cases occur in patients without evidence of heart disease, and in this last group the arrhythmia is often precipitated by severe infection. If the ventricular rate is rapid, digitalis is preferable to quinidine for the treatment of the attack, but with a slower ventricular rate quinidine, 5 grains (300 mg.) two-hourly for six doses, is usually effective. Quinidine should also be used for the prevention of attacks (5 grains [300 mg.] three times a day). In patients without evidence of heart disease failure to control the attack should lead to a search for some cause such as masked hyperthyroidism with a small nodular goitre, or an early bronchial carcinoma irritating or infiltrating the heart muscle.

Only a very small proportion of patients with established atrial fibrillation require quinidine treatment and in the majority quinidine is contraindicated and may be dangerous. If atrial fibrillation occurs in the natural evolution of rheumatic, hypertensive or ischæmic heart disease the arrhythmia will almost certainly recur even if the initial attempt to restore normal rhythm is successful, and quinidine should not be used. Exceptionally in these cases atrial fibrillation may have been unexpectedly produced by an infection and here an attempt to restore normal rhythm with quinidine is justified. In patients with severe mitral stenosis who have had a successful mitral valvotomy it is justifiable to use quinidine postoperatively and these patients may remain in normal rhythm for many years.

Quinidine is useless in the management of atrial fibrillation in untreated hyperthyroidism. When, however, the hyperthyroidism has been successfully treated, either medically or surgically, spontaneous reversion to normal rhythm occurs in about 50 per cent. of cases and in the remainder an attempt should be made to restore normal rhythm. In the postoperative case it is usual to wait for two weeks and if atrial fibrillation persists a course of quinidine should be given.

'Lone' fibrillation may persist in patients who show none of the usual causes for atrial fibrillation and quinidine is often very effective in abolishing the arrhythmia.

The chief risk in quinidine treatment of atrial fibrillation is that of embolism and, although it has been shown that its frequency is no greater in those patients treated with quinidine than in untreated cases, the fear of embolism is always present during treatment. As it is thought that the thrombus which is dislodged to form the embolism is of recent origin, it has been suggested that a course of anticoagulants should be given prophylactically for two to three weeks before quinidine treatment is started. There is no evidence that this procedure, using the anticoagulant drugs at present available, decreases the incidence of either thrombosis or embolism in these patients, although if more effective methods of controlling blood coagulation became available there would be good justification for their use.

If it is decided to use quinidine to treat atrial fibrillation the patient should

first be digitalized and a maintenance dose of digitalis continued throughout the course of quinidine. This is to prevent both the gradual increase in ventricular rate which otherwise occurs before reversion takes place and also the occurrence of a 1:1 ventricular response when the fibrillation waves slow to about 200 per minute. There are several effective ways of administering quinidine for this purpose. It may be given two-hourly for six doses daily, starting with a dose of 200 mg. and increasing to 400 mg. but it is rarely necessary or safe to increase the total daily dose above 2.5 g. This method produces a fairly high quinidine blood level throughout the twenty-four hours but in resistant cases a higher peak level may be effective and this can be achieved by giving the same total daily dose divided into only three separate doses given at two-hourly intervals each day. In either case maintenance quinidine treatment (300 mg. three times a day) is continued for one month following successful conversion and digitalis is discontinued. In extremely resistant cases heroic dosage of quinidine has been used, treatment being controlled by electrocardiogram and estimation of quinidine blood levels. The great risk of toxicity and the high probability of relapse in these cases rarely makes it worth while exceeding the doses stated.

ATRIAL FLUTTER

The drug of choice in the treatment of atrial flutter is digitalis which will either restore normal rhythm or cause reversion to the more easily controlled atrial fibrillation. If atrial fibrillation persists an attempt to restore normal rhythm with quinidine should be made as already described.

SUMMARY AND CONCLUSIONS

Quinidine is a myocardial depressant and although it occasionally causes toxic reactions, it is a useful drug for the treatment of the cardiac arrhythmias.

It is effective in the suppression of ectopic beats and is useful in the prevention and treatment of the various types of paroxysmal tachycardia.

In established atrial fibrillation caused by rheumatic or ischæmic heart disease or thyrotoxicosis, quinidine should only occasionally be used as, unless the underlying cause can be removed, the arrhythmia will usually recur.

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PROCAINAMIDE

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PROCAINAMIDE hydrochloride has the empirical formula, $C_{13}H_{21}N_3O$. It differs from procaine only by the presence of an amide grouping (–CO.N.H–) in place of an ester grouping (–CO–). It is a crystalline powder, soluble and reasonably stable in water but insoluble in aqueous alkaline solutions.

Its actions are qualitatively similar to those of procaine but the amide has two advantages. In the first place, it is more stable as it is less readily hydrolysed by plasma esterases, and has therefore a longer duration of action. Secondly, the cardiac effects predominate over the stimulatory action on the central nervous system. The cardiac actions are identical with those of quinidine. The drug is a cardiac depressant and excitability of both the atrium and the ventricle is depressed, and conduction in the atrium, bundle of His and ventricle is slowed. The refractory period is prolonged, that of the atria more than the ventricles. The occasional accelerating effect of procainamide on the heart rate suggests that the drug also possesses anticholinergic properties. Electrocardiographic changes show widening of the QRS complex and prolongation of the P-R and Q-T intervals.

Absorption and excretion.—Following oral administration absorption is rapid and complete. Peak plasma levels are attained in about an hour, comparable to those obtained by intravenous administration of a similar dose. After intramuscular injection peak levels appear in fifteen to thirty minutes. Subsequently there is a slow decline, although a significant level is still present after six hours. On regular oral dosage, a fixed plasma level is present after forty-eight to seventy-two hours, when absorption and excretion are balanced. Fifty to sixty per cent. of the drug is excreted unchanged in the urine.

TOXICITY AND SIDE-EFFECTS

Hypotension rarely develops after oral administration but is fairly common following intravenous injection and, although usually mild and transient, severe falls of pressure can develop. For this reason it is advisable to have a pressor agent to hand, such as methoxamine or mephentermine, when giving the drug intravenously. A dose of 10 to 20 mg. of either drug intramuscularly, or even intravenously, can be given immediately if the need arises. The effects on the central nervous system are slight but occasionally patients have experienced mental confusion, hallucinations and depression. Agranulocytosis has been reported but only in patients on long-term treatment for more than six weeks. Patients on such treatment should be instructed to report immediately any episodes of sore throat or sore mouth.

Hypersensitivity to procainamide can occur and may consist of chills, fever and urticaria. Cross-sensitivity to procaine usually exists. Asthmatic attacks are said to have been precipitated by the drug in asthmatic individuals

and caution is necessary when administering the drug to patients with a history of asthma. This complication is rare and an asthmatic history does not contraindicate the use of the drug, particularly in cardiac emergencies. (Aminophylline should be available when using procainamide in these circumstances.) With large doses of procainamide, anorexia, nausea, vomiting and diarrhœa are prone to occur.

In relation to the effects on the heart itself, as with quinidine therapy in atrial fibrillation or atrial flutter, the ventricular rate may suddenly increase

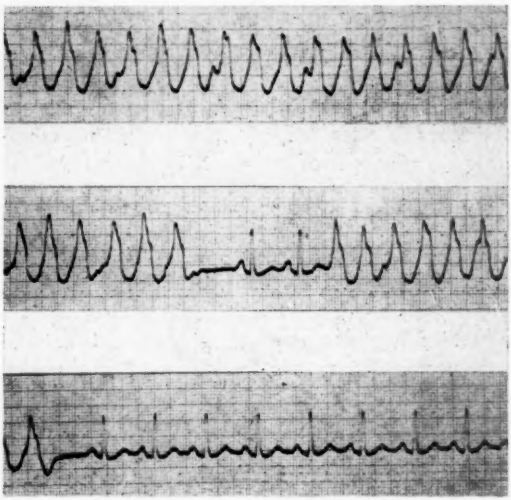

FIG. 1.—Electrocardiographic record (lead II) of response of paroxysmal ventricular tachycardia to procainamide. (a) Pre-treatment record. (b) Record taken after 800 mg. of procainamide, showing short run of sinus rhythm. (c) Record taken after 950 mg. of procainamide, showing established sinus rhythm.

as the atrial rate is slowed. Adequate digitalization lessens, but does not abolish, this danger. Ventricular tachycardia may also develop if supraventricular pacemakers are proportionately more depressed. In patients with atrioventricular block, bundle-branch block or severe digitalis intoxication, further depression of conduction may result in ventricular asystole or ventricular fibrillation.

THERAPEUTIC USES

Procainamide has been widely used in the treatment of cardiac arrhythmias. In general the effectiveness of the drug parallels that of quinidine, but a patient may respond to treatment with one of these drugs despite failure to respond to the other.

Ventricular arrhythmias.—The most favourable results have been reported in ventricular arrhythmias, excepting those due to digitalis intoxication. Ventricular extrasystoles and paroxysmal ventricular tachycardia are

abolished within a few minutes of intravenous injection, or one to two hours after oral administration. Maintenance therapy may be necessary in some cases and recurrences usually respond as promptly as the initial episode.

Figure 1(a) shows an episode of paroxysmal ventricular tachycardia in a thirty-year-old man. Procainamide was given intravenously with continuous recording of the electrocardiogram. After 800 mg., given over a period of about ten minutes, brief bouts of sinus rhythm appeared (b). When a total of 950 mg. had been injected normal sinus rhythm became established (c).

Supraventricular arrhythmias.—The results are not as satisfactory as with ventricular arrhythmias, and usually the drug is used only after other measures have failed. In atrial flutter the slowing of the atrial rate may result in a dangerous increase of heart rate if a 1 to 1 A-V response develops. This risk is lessened by preliminary digitalization. Procainamide is not the drug of choice in reverting atrial fibrillation to sinus rhythm, and although it succeeds in a number of cases, it is less effective than quinidine.

Prophylactic uses.—Patients with recurrent arrhythmias who respond to treatment with procainamide are often kept on long-term treatment with the drug, as a prophylactic measure, for periods of many months. In these patients care regarding agranulocytosis is necessary. The drug is also used in patients undergoing cardiac and thoracic surgery as a preventive measure.

DOSAGE AND ADMINISTRATION

Procainamide is preferably given by mouth, and intravenous administration is reserved for medical emergencies. The intramuscular route is only of value in patients who are unable to take the drug by mouth. Intravenous administration of the drug should only be carried out under direct electrocardiographic control with a direct writing instrument. In addition, frequent blood-pressure readings should be recorded.

The drug is available in 10-ml. ampoules containing 100 mg. of procainamide in each millilitre. The rate of injection should not exceed more than 100 milligrams a minute and no more than 1 gramme should be given at a time. It is usually necessary to dilute the drug to permit greater control of the infusion rate, and the simplest way is to add three parts of saline to one part of procainamide, to give a 2.5 per cent. solution. For practical purposes 5 ml. of the drug (500 mg.) can be drawn up into a 20-ml. syringe and the remaining volume filled with saline. Each millilitre then contains 25 mg. of procainamide and 4 ml. (100 mg.) can be slowly given over each one- to two-minute period. Total doses of over 1.5 g. have been given at one injection in a few cases, but the average effective dose is about 300 mg.

For oral treatment it is common to begin with a 1-gramme dose and then continue with further doses of 0.5 g. every two hours, until the abnormal rhythm is abolished or toxic symptoms develop: nausea, vomiting, sweating and prostration. Doses of up to 6 to 8 g. a day have been used. Maintenance oral therapy may be necessary to prevent a recurrence of the arrhythmia. The dose required varies from 1 to 4 g. a day and can only be decided in the individual patient by clinical trial.

CHLOROQUINE IN THE MANAGEMENT OF CARDIAC ARRHYTHMIAS

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CHLOROQUINE is one of the large series of quinolines investigated in the attempt to find a more effective and less toxic suppressive agent in malaria. Its chemical formula is 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline. The main action of chloroquine is exerted on certain pathogenic parasites, including plasmodia and amœbæ. Chloroquine and other antimalarial drugs, such as quinine, quinidine, and mepacrine, have long been known to have a definite action on the heart and have been used for the treatment of cardiac arrhythmias.

EXPERIMENTAL DATA

Experiments in animals have shown that chloroquine exerts a more effective antifibrillatory action in the heart than quinidine (Arora *et al.*, 1955). The fibrillation-combating properties of chloroquine were studied by Arora and his colleagues (1956) in mongrel dogs with atrial flutter induced by the injury-stimulation procedure, using quinidine sulphate and procainamide as reference standards. The average total dose of chloroquine producing reversion of the flutter to normal sinus rhythm was 6.2 mg./kg., whilst doses of 21.1 mg./kg. of quinidine sulphate and 33 mg./kg. of procainamide were required. Hess and Schmidt (1959) have shown that intravenous injections of chloroquine, in doses of 0.2 to 1.5 mg./kg., are capable of terminating aconitine-induced atrial fibrillation in the open-chest dog preparation. These injections had little effect on the systemic blood pressure, despite marked vasodilating action on intra-arterial administration and a depressant effect on ventricular contraction. In contrast, comparable doses of quinidine produced a marked fall in systemic blood pressure. Chloroquine and quinidine were equally effective in depressing the resting excitability of the isolated cat papillary muscles. On the other hand, compared with quinidine, chloroquine decreased conduction velocity very little, and the muscle recovered from the chloroquine-induced depression but showed little recovery from the quinidine effects.

Chloroquine is almost completely absorbed from the gastro-intestinal tract. Only small amounts are observed in the stools, and only 10 to 20 per cent. is found unchanged in the urine. From two hundred to seven hundred

times the plasma concentration may be found in the liver, spleen, kidney, and lung (Goodman and Gilman, 1955).

In experiments by Hess and his colleagues (Hess and Haugaard, 1956, 1958) with rat-heart slices and homogenates, it was found that, whilst quinine and quinidine strongly depressed oxygen uptake and glucose utilization, chloroquine (and procainamide) had no such depressant effect. Sanabria and his colleagues (1959), however, in studying the actions of chloroquine on the enzymes of the conduction system in the dog's heart, have found that an inhibition of succinic dehydrogenase results after intravenous administration of chloroquine that is not apparent after injections of quinidine and procainamide. Since the enzyme acts in the Krebs cycle on transformation of succinic acid to fumaric acid, it is assumed that inhibition of this enzyme renders the energy required for conduction of the cardiac impulse unavailable. The antifibrillatory action of chloroquine may be attributed to this inhibiting effect.

CLINICAL DATA

Chloroquine has been employed at various times in the treatment of arrhythmias as an alternative drug to quinidine. It has been administered orally, intramuscularly, and intravenously. Burrell and Martinez (1958) found that chloroquine, as well as hydroxychloroquine, was effective in the therapy of cardiac arrhythmias. The side-effects appeared to be fewer and less pronounced than after the use of quinidine and quinine. When chloroquine was administered intravenously in two patients with atrial fibrillation, Sanghvi (1956) found that the fibrillation changed to atrial flutter. Slowing of the atrial rate appears to be due to a vagolytic action and an increase in the refractory period similar to that of quinidine.

Sanabria (1955) collected 35 cases of arrhythmias treated with chloroquine and observed favourable effects in only about one-half of the cases studied. In addition, there was a relatively high incidence of gastro-intestinal symptoms: e.g. nausea and vomiting. On the other hand, Ch'en and Chou (1959) reported a large measure of success in the treatment of 13 patients with various types of cardiac arrhythmia. In six of the patients, the ectopic rhythm disappeared, and there was marked improvement in five others. In his experience, cases which demonstrated a poor response to chloroquine also showed a poor response to procainamide and quinidine. Again, the side-effects were chiefly gastro-intestinal and subsided within two to three days after the drug was discontinued.

In my own experience, when the effects of chloroquine and quinidine were compared in the same patients under similar conditions, chloroquine was found to be less dependable in both the abolition and suppression of ectopic rhythms. Furthermore, some investigators (e.g. DiPalma, 1960) are discarding its use because of the rapid development of tolerance.

The initial dosage is usually 1 gramme daily, which is increased by 0.25 gramme every third day until termination of the arrhythmia or gastro-intestinal side-effects necessitate cessation. Doses of 0.25 to 1 gramme daily have been used in the maintenance of some patients for as long as a year without noticeable side-effects. The intramuscular dose is 20 mg., administered every four to six hours.

TOXIC EFFECTS

The toxic effects of both chloroquine and quinidine are quite similar, but chloroquine appears to be less toxic and better tolerated than quinidine. Large doses may cause mild and transient headache, gastro-intestinal complaints, and pruritus. Prolonged treatment causes a lichenoid skin eruption in some patients. Visual disturbances and retinopathy have also been reported after extensive chloroquine therapy (Hobbs *et al.*, 1959). None of these symptoms, however, is serious, and all readily disappear when the drug is withheld.

SUMMARY

Chloroquine is an effective agent in the therapy of cardiac arrhythmias.

The indications for its use are, in a general way, similar to those for quinidine. The untoward and cardiotoxic effects are less marked than those of quinidine.

Experience, however, has indicated that chloroquine is less effective than quinidine in the abolition and prevention of ectopic rhythms.

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DIURETICS IN CARDIOVASCULAR DISEASE

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PERIPHERAL or generalized œdema is a prominent feature of some diseases of the kidney and of cardiac failure and often persists as a residual disability when other symptoms of the causative disorder have been alleviated or subdued. Although the mechanism of production of these two forms of œdema, the dependent œdema of cardiac failure and the generalized œdema of renal disease, are not wholly understood, it is known that different processes of dynamic pathology operate to promote accumulation of fluid in the tissues in each condition. Accordingly, the treatment required in the two types of œdema is different. This article is concerned with the treatment of œdema of cardiac origin and the rational therapeutic approach to this problem illustrates two great principles of therapeutics: first, and preferably, to remove the primary cause of a symptom and, secondly, if the former be not possible, so to influence the disorder of function as to minimize its effects. It is evident, but yet cannot be too strongly emphasized, that the fundamental cause of cardiac œdema is myocardial insufficiency, and treatment by whatever means to alleviate the cause must not be neglected.

PULMONARY ŒDEMA

In cardiac failure œdema may occur in the territory of the pulmonary circulation or the systemic circulation, or both. The dramatic episodes of pulmonary congestion, paroxysmal dyspnœa and pulmonary œdema are due to venous congestion of the lungs caused by unequal efficiency of the two ventricles, when the left ventricle is unable to cope with the load of blood pumped into the lungs by a more efficient and better-filled right ventricle. Pulmonary œdema presents a different immediate therapeutic problem from that presented by systemic œdema, except in one respect. In both forms of cardiac failure the ability of the kidney to remove water from the blood is reduced. Thus the tendency to pulmonary œdema is increased by an increase in the total circulating blood volume which has resulted from fluid retention, and right ventricular output is increased beyond the capacity of the left ventricle to prevent congestion of the lungs.

SYSTEMIC ŒDEMA

When the right ventricle fails, with or without concomitant failure of the left ventricle, the features of congestive cardiac failure—venous congestion, hepatomegaly and œdema—appear and dominate the clinical picture. This triad provides the classical indications for treatment with digitalis glucosides.

Even in the absence of atrial fibrillation digitalis will often relieve congestive failure but, on account of the well-known pharmacological characteristics of the digitalis glucosides, the beneficial effects of this treatment do not appear for some time, and it is usual and advisable to associate with digitalis a diuretic which will relieve congestion by reducing the volume of blood in the vascular compartment. An additional reason for administering diuretics in association with digitalis has been suggested by Brenner (1959): namely, that, whilst the œdema of cardiac failure is apparent in the subcutaneous tissues, the internal organs including the heart are also œdematous and are anatomically and biochemically abnormal. Relief of this œdema may enable digitalis and other measures to exert their effect on a more normal organ. In congestive cardiac failure, even when considerable symptomatic improvement has been achieved, systemic œdema is often a residual disability which can be alleviated only by the use of diuretics. Diuretics must therefore be regarded as symptomatic remedies modifying in a favourable way a disorder of function which has its origin in the disorder of a remote organ, and should be regarded as adjuvant therapy rather than as fundamental therapy.

URINE FORMATION

There are two stages in the secretion of urine by the kidney. A solution of electrolyte is filtered through the glomerulus and then modified in volume and composition by selective reabsorption in the renal tubule. Since most potent diuretics useful in the treatment of cardiac œdema act on the tubular epithelium to modify its handling of the glomerular filtrate in such a way as to increase the amount of urine reaching the renal pelvis, it follows that in the absence of glomerular filtration a diuretic can have no action. Since different diuretic drugs act on different tubular reabsorptive mechanisms they tend to produce characteristic changes in the electrolyte composition of the urine and consequently, and secondarily, of the blood and tissues.

THE MODE OF PRODUCTION OF ŒDEMA IN CARDIAC FAILURE

The mechanism whereby œdema is produced in cardiac failure is not yet well understood, but changes in circulatory dynamics which occur in congestive cardiac failure can be seen as a logical sequence of events creating and maintaining the œdematous state. Yet the connecting link between early heart failure and the renal changes which lead to fluid retention is not yet known. Speculation and effort to identify this connexion, however, are not idle because, although considerable advances have been made in diuretic treatment, the ideal therapeutic regime for chronic congestive failure awaits a fuller understanding of the primary cause of œdema in congestive failure. Increased capillary permeability resulting from tissue anoxia is an unlikely cause since the protein content of œdema fluid is low, having the characteristics of a transudate; further, œdema develops in the absence of

anoxæmia. Raised hydrostatic pressure from venous congestion and increased venous pressure may cause transudation, but it is known that in other conditions associated with raised venous pressure œdema may not occur even with degrees of intravenous pressure much higher than those attained in severe congestive failure.

As the heart begins to fail the renal blood flow is reduced, but it has been shown that glomerular blood flow and filtration rate fall disproportionately to the fall in cardiac output. The amount of extracellular electrolyte filtered falls to a level below which the renal tubule cannot reduce its reabsorptive capacity, and most of the filtrate is reabsorbed; sodium chloride and fluid thus retained leads to an expanded extracellular fluid volume and raised venous pressure. This renal effect of cardiac failure is not due to renal venous congestion since it can be demonstrated even in the earliest stages of failure. Similarly, the renal reduction in blood flow seems to occur independently, and in advance of a significant fall in cardiac output. Indeed, it can be shown to occur in cardiac failure associated with an abnormally high cardiac output as, for example, in congestive failure associated with such conditions as thyrotoxicosis, severe chronic anæmia and pulmonary heart disease, although in the latter condition other explanations have been suggested (Campbell and Short, 1960). Reduction in glomerular filtration and excessive absorption of sodium and water in the renal tubule in cardiac failure provide a rational basis for diuretic therapy, yet it is the end-result of a mechanism, the explanation of which is incomplete and other mechanisms must be sought to explain discrepancies.

It seems likely that a complex neurohormonal process plays a part in the production of œdema. This is shown, for example, by the fact that abnormally high amounts of anti-diuretic hormones and the sodium-retaining hormone, aldosterone, appear in the urine during episodes of congestive cardiac failure. Disturbances in the function of hypothetical volume receptors located in the atria have been adduced to explain the earliest changes in renal circulatory dynamics in early cardiac failure (Love *et al.*, 1957). Such speculation is worth while because the object of diuretic therapy is not only to promote the excretion of œdema fluid, but also to prevent the formation of œdema. Whatever pathological subtleties are involved in the primary causation of cardiac œdema, whether it be the obtrusive œdema of predominant right heart failure or the more latent œdema of left heart failure, the total body fluid is increased, total sodium is much increased (although the concentration of sodium and of chloride in serum may be lower than normal as a result of dilution), and the potassium concentration of the serum may be much increased.

CLASSIFICATION OF DIURETICS

Diuretic drugs are employed to promote the renal excretion of accumulated water and sodium salt, and it is held by some that diuretic therapy alone is

adequate to control all the features of congestive cardiac failure without recourse to the more fundamental treatment of myocardial failure with drugs of the digitalis group. Whilst it is true that in some cases of predominant right heart failure, and perhaps more cases of left heart failure, the effect of diuretic therapy is similar to that of digitalis, it is certain that the primary fault lies in myocardial insufficiency, and if this defect can be improved by digitalis glucosides, such treatment should always be employed in the first instance and supplemented by diuretics.

The diuretic drugs which are available for the treatment of cardiac œdema may act in different ways and some have complex actions which should be recognized and related to the renal functional disturbance of cardiac failure if they are to be effectively employed. It is convenient to classify diuretics according to their predominant mode of action.

(1) *Diuretics which increase glomerular filtration*
  (a) Digitalis glucosides
  (b) Acidifying salts; e.g. ammonium chloride

(2) *Diuretics which prevent or reduce sodium reabsorption in the renal tubules*
  (a) Xanthine diuretics; e.g. theophylline
  (b) Amino-uracil diuretics; e.g. aminometradine
  (c) Carbonic anhydrase inhibitors; e.g. acetazolamide
  (d) Mercurial diuretics; e.g. mersalyl
  (e) Benzthiadiazines

(3) *Substances which antagonize sodium-retaining hormones*
  Spirolactones

This classification does not include all diuretic substances but in the interests of simplicity is restricted to drugs which are relevant to the treatment of cardiac œdema.

XANTHINE DIURETICS

The xanthines—caffeine, theobromine, theophylline and aminophylline—have a long and reputable history in the treatment of cardiac failure. The value of the former three substances, which for long were used as oral diuretics in cardiac œdema, is limited by a tendency to cause unpleasant side-effects, but they undoubtedly promote diuresis, partly by inhibiting tubular reabsorption of sodium and water. They have now been superseded by more effective compounds. On the other hand, aminophylline, when given by slow intravenous injection, has actions which are not seen when the xanthines are given by mouth. It relaxes the smooth muscle of vessels and increases cardiac output, in addition to affecting renal tubular absorption. In this way, by increasing glomerular filtration and affecting tubular reabsorption it is a potent diuretic. It has often been noted that in severe cardiac failure, when œdema may be resistant to mercurial diuretics, the combined use of parenteral aminophylline and mersalyl often produces a brisk diuresis. Aminophylline may be given with advantage by slow intravenous injection in doses of 250 to 500 mg. two hours after the intramuscular injection of

mersalyl. The drug can also be given orally as 100-mg. tablets B.P. or by rectal suppository containing 360 mg. of aminophylline, but by these routes absorption is uncertain.

AMINO-URACIL DIURETICS

Aminometradine and amino*iso*metridine are effective diuretics when given orally. They act by inhibiting the reabsorption of sodium by the renal tubule and thus promote the excretion of sodium chloride, potassium and water. The effect on the composition of the urine is roughly similar to that of the more recently introduced benzthiadiazines but quantitatively much less. The amino-uracils have also a rather marked tendency to cause gastric irritation and have in consequence been superseded by the newer benzthiadiazine derivatives.

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide.—This substance, related to the sulphonamide group of drugs, inhibits carbonic anhydrase in the renal tubule and causes diuresis by preventing the reabsorption of bicarbonate so that increased amounts of bicarbonate, potassium and sodium are excreted and an alkaline urine is formed. Loss of bicarbonate leads to systemic acidosis when no further bicarbonate is available for excretion; the diuretic action of acetazolamide then ceases. The action of this drug is thus self-limiting and of short duration and it has been largely abandoned as a diuretic for continuous use, in favour of substances with a more prolonged action.

MERCURIAL DIURETICS

Inorganic mercury in the form of calomel was used as a diuretic for centuries before the accidental discovery of the dramatic diuretic properties of the organic compounds of mercury. At the present time these are perhaps the most potent and rapidly acting diuretics available. In organic combination mercury is rapidly excreted and after an effective therapeutic dose the diuretic effect appears within two hours, reaches a maximum in about eight hours and is as a rule over by twelve to twenty-four hours. It is known that mercurial diuretics act exclusively on reabsorption of electrolyte in the proximal tubule, and it is thought that the effect is primarily to inhibit the reabsorption of chloride so that the cation sodium is excreted in combination with chloride, water being retained in the tubule by osmotic action. The bicarbonate content of the urine is not increased and, since tubular mechanisms for the excretion of potassium seem to be rather specifically inhibited by mercurials, sodium chloride is the predominant salt in the urine and hypokalæmia does not tend to occur. Because chloride reabsorption is preferentially inhibited, the blood may become depleted of this ion so that after prolonged treatment with mercurial drugs hypochloræmic alkalosis may occur. In these circumstances the glomerular filtrate will contain sufficient

chloride to enable the mercurial to exert its diuretic effect, and this is one of the causes of mercury-resistant œdema. It is well known that the diuretic effect of mercury compounds can be enhanced and that diuresis can often be induced in patients who have become refractory to its action by the prior administration of 2 grammes of ammonium chloride.

From what has been said it will be apparent that the action of organic mercurials is dependent on an adequate filtered load of sodium chloride. Since the filtered load equals the filtration rate multiplied by plasma chloride, it follows that if the glomerular filtration rate is seriously reduced in cardiac failure even if the plasma level of chloride is normal or high, organic mercurials may fail to induce diuresis. For this reason efforts to improve renal circulation by the use of digitalis and aminophylline may have gratifying results in refractory œdema.

Numerous organic compounds of mercury are available for use as diuretics. They are most effective when given by deep intramuscular injection; intravenous administration is to be deprecated since severe and fatal reactions may result. In this country, injection of mersalyl B.P., which contains 100 mg. of sodium mersalyl in 2 ml., is official and is not excelled in efficacy by the many proprietary preparations available. In the past, preparations of organic mercurial compounds have been given by mouth. Whilst they have the advantage of convenience, they cause gastro-intestinal irritation, and, since the amount of mercury required is large, present the risk of systemic mercurial poisoning. The diuretic effect of such preparations is, in any case, limited and they have been superseded by orally active diuretics which are more effective and less dangerous.

THE BENZTHIADIAZINES

This group of substances comprises a number of potent diuretics which are effective when given by mouth. The first of these to be introduced was chlorothiazide, which is of considerable value in the treatment of cardiac and other forms of œdema. Drugs of this class have the great advantage of permitting self-administration but they do not replace mersalyl in the initial treatment of severe congestive failure or left heart failure. They are, however, valuable adjuncts and should in the main be used in the treatment of the milder forms of œdema and to prevent the recurrence of fluid retention rather than to relieve the severe and acute manifestations of this condition. The benzthiadiazines act on the renal tubules to inhibit the reabsorption of sodium and chloride and to a lesser extent of potassium and bicarbonate. They do not affect the renal blood flow nor do they increase the glomerular filtration rate, so that the diuresis caused by such substances is an osmotic consequence of the effect on tubular reabsorption of electrolyte. Unlike acetazolamide, they do not cause significant loss of bicarbonate so that systemic acidosis does not occur.

The renal excretion of potassium, however, is considerably increased and

may lead to a clinically significant fall in the serum content of this element. This is particularly liable to happen when the drug is given frequently over a prolonged period to patients who are severely œdematous and whose illness renders them unable to take a full normal diet. Apart from the effects of potassium depletion, side-effects are uncommon, but some have been recorded following the use of the older drugs of this class, and it remains to be seen if more recently introduced substances will occasionally show similar toxic actions when more patients have been treated. The toxic effects which have been recorded include photosensitization, skin rashes, and allergic manifestations including purpura and agranulocytosis (Fitzgerald, 1960). Blood uric acid may be raised and attacks of gout precipitated, occasionally diabetes mellitus may be aggravated or, where latent, become manifest in susceptible patients. In patients with extreme impairment of liver function hepatic coma may be precipitated.

It has been found that this group of diuretic drugs has an interesting effect in potentiating the action of ganglion-blocking agents used in the treatment of hypertension and also in augmenting the effect of digitalis on the heart. Several explanations for these effects are possible and the mechanism is not yet quite clear. Nevertheless, modifications of the dose of digitalis or antihypertensive drugs may be necessary when benzthiadiazines are used concurrently.

Since the introduction of chlorothiazide several chemically similar compounds have been introduced. They do not differ from chlorothiazide in their pharmacological effect on the renal tubule and thus cause diuresis in the same way. The quantity of the newer derivatives required to produce a degree of diuresis equal to that caused by a given dose of chlorothiazide is, however, smaller. They are more slowly excreted than chlorothiazide so that the diuretic effect in equi-potent doses is less intense and more prolonged. This difference in diuretic potency would be of importance if the cost of an effective dose of the newer substances were proportional to its size, but equally effective doses of these substances are about equal in cost. The longer duration of action of the newer derivatives may be a convenience but it should be remembered that in the treatment of œdema the quantity of fluid excreted is the best measure of the efficiency of a diuretic. The average effective dose of this group of substances varies from 5 mg. in the case of bendrofluazide to 500 mg. for chlorothiazide. Increasing the dose beyond these limits does not proportionately increase sodium and water excretion so that, other things being equal, a drug with a small dose offers little advantage to the patient.

There is no evidence to suggest that a patient who fails to respond to one member of the series will respond better to another. This is only to be expected since the mode of action of these drugs is similar. For the same reason claims that the urinary excretion of potassium is less with one drug than another have generally not been supported by experience so that, when

these drugs are used over prolonged periods, administration should be intermittent, the diuretic being given on two or three days in the week or alternate days depending on the individual needs of the patient. The risk of hypokalæmia depends upon such factors as degree of œdema, food intake and frequency of administration. In general, supplementary potassium should be given in the form of a mixture containing 0.5 gramme of potassium citrate and 0.5 gramme of potassium chloride in water with a flavouring agent. This mixture can be given thrice daily on days when the diuretic is not being taken.

The recommended dose of the benzthiadiazines per twenty-four-hour period is shown in table 1, together with the usual duration of effect. As with

Preparation	Dose	Duration of effect
Chlorothiazide	500 to 1000 mg.	6 to 8 hours
Hydrochlorothiazide	50 to 100 mg.	10 to 12 hours
Hydroflumethiazide	50 to 100 mg.	10 to 12 hours
Bendrofluazide	5 to 10 mg.	24 hours
Chlorthalidone	100 to 200 mg.	72 hours

TABLE I.—Comparable doses and approximate duration of diuretic action of the benzthiadiazines.

all drugs there is an individual variation in response, and doses may have to be varied within limits in different patients and in the same patient from time to time. In the case of the shorter-acting drugs a better diuretic effect is obtained with divided doses, whereas a single daily dose of the longer-acting compounds may be sufficient. Since effective doses of the benzthiadiazines cause considerable sodium excretion it may not be necessary to advise rigid limitation of salt intake, but in the maintenance of the œdema-free state it is probably wise to recommend moderation in salt intake.

SPIROLACTONES

Aldosterone is the salt-retaining hormone of the adrenal cortex. Its physiological function is to promote the reabsorption of sodium and the secretion of potassium by the renal tubules. It is thus of primary importance in controlling the volume of the body fluids. The effects of aldosterone deficiency are seen in the dehydration of Addison's disease, and those of oversecretion in rare cases of certain adrenal tumours. Increased production of aldosterone occurs as a physiological response to states of acute dehydration as in hæmorrhage and shock, but there is evidence that in cardiac, renal, and hepatic œdema aldosterone secretion is increased, since abnormally large amounts of the hormone can be recovered from the urine. The increased secretion of aldosterone in œdema must be regarded as a pathological response, as the effects of the hormone in favouring the retention of sodium and water can only aggravate œdema. Thus, if the formation of aldosterone can be inhibited or its effects prevented, sodium loss and water loss with consequent reduction in body fluid would be expected to follow. Aldosterone

production from the adrenal can be prevented only experimentally by such substances as amphenone but the action of aldosterone on the tubule can be inhibited by the administration of steroids similar to aldosterone in chemical structure but lacking its action. These substances displace aldosterone from chemical receptors in the tubule and thus prevent the hormone from producing its characteristic action. Substances of this class are called spirolactones and one of these, spironolactone, has been introduced for clinical use.

When given along with diuretics this substance has been found to be effective in causing diuresis and relieving fluid retention in nephrotic œdema and in ascites in liver disease. It has not been found so effective in resistant œdema of cardiac failure. This is only to be expected since resistant œdema is so often due to deficient glomerular blood flow and filtration, and a substance which acts on the renal tubule will not improve glomerular filtration. Spironolactone is given in divided doses of 400 to 800 mg. daily and it is usual to give the drug alone for a period of four days, and thereafter, while continuing at the same dose-level, to administer an effective daily dose of a mercurial or benzthiadiazine diuretic. For reasons already mentioned it is unlikely that spironolactone will find an important place in the treatment of œdema in cardiac failure, and its high cost renders its use unjustifiable when simpler and cheaper remedies are effective.

ŒDEMA IN PREDOMINANT RIGHT HEART FAILURE

Pure right heart failure is rare; in most cases of congestive cardiac failure some degree of left heart failure exists. Nevertheless, when venous congestion, hepatomegaly, and œdema constitute the presenting features we speak of right heart failure. In this condition there is massive accumulation of fluid in the tissues and the first object of treatment is to promote diuresis to relieve the œdema. Treatment of the primary myocardial insufficiency is essential, despite a recent tendency to rely exclusively on diuretics. Rest and digitalis remain of primary importance.

Mersalyl, given by intramuscular injection in doses of 2 ml. every two or three days depending on the response, is the most rapidly acting and effective diuretic in severe œdema. Each injection should be given in the morning and may with advantage be preceded by administration of 2 grammes of ammonium chloride by mouth. Failure to respond to the first two or three injections of mersalyl should not be unexpected as a diuresis may not occur until renal blood flow has been improved by the beneficial effects of rest and digitalis. If no diuresis is induced after four or five injections the cause may be irreparable cardiac insufficiency but quite often the failure may be due to hypochloræmia, and increasing the dose of ammonium chloride to 2 grammes three times daily may induce a response to the mercurial diuretic. In very refractory cases aminophylline by intravenous injection, 250 mg. in 10 ml. given two hours after the intramuscular

injection of mersalyl, may often lead to diuresis which progressively increases. The administration of 500 mg. of chlorothiazide, or equivalent preparation, either in the morning when mersalyl is given or alternating with it, has been recommended and may indeed lead to copious diuresis, but in resistant œdema this measure is seldom effective when mersalyl alone fails. Intramuscular injections of mersalyl are somewhat painful but the risk of fatal reactions following its intravenous use prohibits this route of administration. Mercaptomerin is less irritating than mersalyl and can be given subcutaneously but it is probably not so potent. Rectal suppositories of mersalyl are irritating and uncomfortable in use and can now be abandoned.

The benzthiadiazine derivatives may be employed in the initial treatment of œdema, and chlorothiazide, in doses of 500 mg. twice daily, or bendrofluazide, 10 mg. in the morning, may be used with good effect if any reason such as that of convenience or the patient's sensitivity makes the use of mersalyl undesirable. If these latter drugs are used in a patient receiving digitalis, it is imperative to prescribe potassium; otherwise the toxic effects of digitalis may be induced. Digitalis poisoning may, of course, occur in any patient who responds dramatically to diuretic therapy and this may be due to concentration of the drug consequent upon loss of body fluid or to other more subtle causes. A rapid and effective diuretic effect may be associated with the development of hiccough and drowsiness, suggesting that uræmia has been induced by dehydration from excessive or over-rapid fluid loss. Similarly, apathy and abdominal cramp suggest sodium depletion. These effects are more common when mersalyl and benzthiadiazine are given concurrently and should be corrected by giving the patient saline to drink. In male patients with prostatic hypertrophy urinary retention may develop during a profuse diuresis if the bladder is allowed to fill and such patients should be advised to void urine frequently after the administration of a potent diuretic.

Even with the diuretic substances at present available it is sometimes necessary to remove fluid from serous cavities by mechanical means. The aspiration of fluid from a hydrothorax, and particularly the relief of ascites by paracentesis abdominis, may enable diuretic drugs to initiate a diuresis. There is, moreover, still a place for the use of Southey's tubes in resistant œdema.

The prevention of œdema and the maintenance of the œdema-free state.—In patients who have recovered from severe congestive failure and in those in whom the condition is incipient, the measures required to prevent œdema must be adapted to the individual needs of the patient, taking into account the degree of cardiac failure, employment, tastes, intelligence, self-discipline and so on. Formerly, attempts were made to prevent sodium accumulation by rigid restriction of salt intake. To this end salt-free food was prescribed or salt was stolen from the intestine by the administration of cation-exchange resins. These measures may still have a place in the initial

treatment of œdema but moderate salt restriction is probably all that is necessary, since the primary action of the benzthiadiazine derivatives is to promote salt excretion. In the prevention of œdema it is essential to support the myocardium in whatever way seems needful and thereafter to use the benzthiadiazine diuretics in doses adequate to maintain the œdema-free weight. For this purpose a long-acting drug such as bendrofluazide, given in doses varying from 2.5 to 5 mg. once daily or on two or three days in the week or even as little as 5 mg. once a week, is suitable. If shorter-acting drugs are deemed preferable, 250 mg. of chlorothiazide given on alternate days may be used. Potassium depletion may develop insidiously in these circumstances and it is advisable to prescribe a potassium supplement equivalent to a gramme of potassium chloride three times daily once or twice during the week.

DIURETIC TREATMENT IN LEFT VENTRICULAR FAILURE

In left ventricular failure œdema may not be clinically prominent but fluid retention contributes to the pulmonary engorgement and reduction in vital capacity. In this condition relatively small increments in blood volume may have catastrophic results. Characteristic of this type of failure are acute episodes of paroxysmal nocturnal dyspnœa and pulmonary œdema. In the treatment of these emergencies blood volume is effectively lowered by venesection and morphine; aminophylline and oxygen play their part, but it is in the prevention of recurrence that diuretics are important. As in right heart failure, treatment should begin with mersalyl and continue with an oral diuretic, although this is not obligatory since relatively small diuresis may be adequate with other measures to relieve dyspnœa and prevent nocturnal dyspnœa.

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VASODILATORS IN CARDIOVASCULAR DISEASE

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In any consideration of vasodilators in cardiovascular disease, pride of place must be given to their use in angina pectoris.

VASODILATORS IN ANGINA PECTORIS

Amyl nitrite was introduced for the relief of cardiac pain by Brunton (1867) and nitroglycerin by Murrell (1879). Today, nearly a century later, these two drugs remain at the head of the list of available remedies. The first use of amyl nitrite was based on the theory that angina pectoris is provoked by a rise in arterial blood pressure and that it should therefore be relieved by any drug which produces a fall in blood pressure. This theory was not correct but there are many other instances of advances in therapy based on fallacious premises. Although today we may have a more correct idea of the way in which cardiac pain arises, we cannot yet claim that our therapy has a very firmly established theoretical basis. Indeed, it is largely pragmatic. This is because the pharmacological study of the effects of drugs on the coronary circulation is an extremely complex problem and the experimental methods available must take account of a large number of interacting factors.

Observations on the effect of drugs on the coronary circulation have been made on the isolated perfused mammalian heart in ventricular standstill, in ventricular fibrillation and while beating, on the heart-lung preparation and on the whole animal, anæsthetized and unanæsthetized. Coronary flow has been estimated in various ways such as collection of coronary sinus outflow, direct measurement within a coronary artery by different types of flow-meter and nitrous oxide uptake in the heart (Wégria, 1951). By the use of these experimental methods many drugs can be shown to cause an increase of flow in the coronary arteries, although it is not always clear how this increase is brought about: whether by an increase in the coronary perfusion pressure, by dilatation of the coronary arteries or by a change in the 'extravascular support' exerted on the coronary arteries by the myocardium. Apart from these direct determinants of coronary flow, other effects of the drug have to be reckoned with: for example, those on the general arterial blood pressure, on the central nervous system and on the work or metabolism of the heart.

Even when it can be shown experimentally that a drug will produce an increase in coronary flow it does not necessarily follow that it would relieve angina pectoris in man. Relief of cardiac pain depends upon the net result of all the various effects of the drug and if, for example, it were to increase the work of the heart proportionately more than it increases coronary flow the

net result might be to aggravate the symptoms. This is the case with adrenaline, which will increase coronary flow in experimental animals (Essex *et al.*, 1940), yet aggravates cardiac pain in patients with coronary disease.

A clear distinction must be made between the pain of myocardial tissue damage (infarction) and that of functional myocardial ischæmia (angina pectoris). It is only in the latter that relief may be given by vasodilator drugs. The ideal drug for the treatment of angina would be one which could dilate the coronary arteries without producing any other effects on the circulation. No such drug has yet been discovered. All the available drugs exert multiple effects, and however valuable experimental studies may be in the development of new drugs, the final test of their value is clinical trial in human patients. Careful studies of exercise tolerance in patients suffering from angina have confirmed the value of the nitrite group, especially nitroglycerin (Wayne and Laplace, 1933-34). Few of the many other drugs found to increase coronary flow in animals have survived clinical test and most of them have fallen into disuse.

THE NITRITE GROUP

This group embraces both nitrites and nitrates. Sodium nitrite has now largely gone out of use and the only two members included in the *British National Formulary* are glyceryl trinitrate (nitroglycerin, trinitrin) and amyl nitrite. There is also a number of proprietary preparations, most of which contain pentaerythrityl tetranitrate ('mycardol', 'peritrate') and are claimed to exert an effect of longer duration than that of nitroglycerin. There are also some proprietaries containing octyl nitrite for use as alternatives to amyl nitrite.

The most valuable drug for the relief of angina pectoris is unquestionably *nitroglycerin*, available as glyceryl trinitrate tablets B.P., 1/130 grain (0.5 mg.) and 1/100 grain (0.6 mg.). The tablets are now constituted with mannitol as base in place of the former chocolate base and are less liable to deteriorate in storage but are best used within three months of manufacture.

They must be allowed to dissolve in the mouth, as they have very little effect when swallowed. Patients should be made aware of this when they are first prescribed. When absorbed from the mouth the drug is often effective in three to five minutes and may act for twenty to forty minutes. These qualities must be borne in mind if the best use is to be made of nitroglycerin. It is not effective as a sustained-action drug and cannot be relied upon to prevent anginal attacks throughout the day. On the other hand, it is rarely rapid enough in its action to relieve an anginal attack once this has begun. It is best used by a system of intelligent anticipation, a tablet being taken before any necessary exertion or emotional stress which the patient knows is likely to provoke an attack of pain. In this way it can be used to protect the patient during certain phases of his daily activity: for example, his journey to or from work, or a public speech, and with a little guidance most patients can make very effective use of it. Dosage should be the

minimum required to prevent pain, beginning with half a tablet (0.2 to 0.3 mg.) two to four times daily. Patients must be warned not to use the drug to allow exertion of harmful degree.

Amyl nitrite, available in glass capsules for inhalation, containing 3 minims (0.2 ml.) and 5 minims (0.3 ml.), is effective for the quick relief of an established anginal attack but its action is of brief duration and its pungent odour and its side-effects (flushing, throbbing headache and faintness) make it much less useful than nitroglycerin. Proprietary inhalers containing octyl nitrite have few advantages over amyl nitrite.

The search for a long-acting nitrate preparation has not been very successful. Slow-release tablets, either of nitroglycerin or pentaerythrityl tetranitrate, have been disappointing, probably because the drug, when gradually absorbed from the alimentary canal through the portal system, is destroyed in the liver before it can attain an adequate concentration in the blood for action on the coronary arteries. All nitrite group drugs may cause headaches, especially if used too often.

OTHER VASODILATORS IN ANGINA PECTORIS

Among the numerous drugs which have been shown to increase coronary flow in experimental animals, the ones most used for the treatment of angina pectoris have been the xanthine group, especially aminophylline (theophylline with ethylenediamine), papaverine and khellin. *Aminophylline* is stated to benefit some patients but it has to be used in full dosage (0.3 g. four-hourly) and few patients can tolerate this dosage without nausea or vomiting. *Choline theophyllinate* ('choledyl') is said to be better tolerated but there are conflicting reports of its value. *Papaverine* is one of the alkaloids of opium. It has little analgesic or narcotic effect and its general vasodilator action is well established. It will increase coronary flow in experimental animals but there is little clinical evidence of its value in angina pectoris. *Khellin* was introduced by Anrep and his co-workers (1949) and at first aroused a great deal of interest. A number of clinical reports indicated that it was of value in the treatment of angina but the later more rigidly controlled studies have not supported this claim and it is now little used. It also causes nausea in some patients. Whatever value some of these drugs may have, it can fairly be said that none of them is equal to nitroglycerin.

VASODILATORS IN PERIPHERAL VASCULAR DISEASE

In 1921, Schäffer suggested the use of papaverine for the treatment of traumatic arterial spasm in gunshot wounds of the limbs and the same drug was introduced by Denk (1934) for the treatment of arterial embolism. During the past twenty years many new vasodilators have been produced and a number of them have been shown to cause increase of peripheral blood-flow in the intact limbs of experimental animals and man. Most of these vasodilators have been used in peripheral vascular disease but to assess their value we must first examine the theoretical basis for their use.

Peripheral vascular diseases fall into two main groups: (1) occlusive disorders (for example embolism or arteriosclerotic intimal disease); (2) vasospastic disorders such as Raynaud phenomenon and acrocyanosis. The theoretical basis for the use of vasodilators is not the same in these two groups.

ARTERIAL EMBOLISM

Many clinicians hold that the ischæmic effects of arterial embolism are only partly due to the occlusion of the arterial trunk by the embolus, and that they may be aggravated by a state of active arterial spasm, excited in the peripheral field of the occluded artery and in its collaterals. Denk's original use of papaverine was based on this view and other vasodilators have also been widely used. In fact, the evidence for arterial spasm in embolism is not very convincing (Jacobs, 1959). Apart from any effect on possible arterial spasm, vasodilators have been used with the aim of counteracting sympathetic vasomotor tone in the collaterals and so allowing an increased flow into the ischæmic part of the limb. Unfortunately, if vasodilators be administered in dosage adequate for this effect they will also produce general vasodilatation elsewhere in the body and the resultant diversion of blood-flow and fall of blood pressure may well reduce flow in the collaterals rather than increase it. In order to avoid this difficulty, vasodilators have been administered by intra-arterial injection (Edwards *et al.*, 1952). In normal human limbs an increase in peripheral blood-flow can be produced in this way, using doses too small to cause any general effect (Duff, 1959). It cannot, however, be assumed that this method will be effective in an ischæmic limb, for the conditions there are quite different. As can be demonstrated by the phenomenon of 'reactive hyperæmia', ischæmic tissues are normally saturated with natural vasodilator metabolites and their blood vessels are already fully relaxed. It is hardly conceivable that any further vascular relaxation could be produced there by administering vasodilator drugs. Moreover, the use of general vasodilators may impose extra strain on a diseased heart. If any attack is to be made on sympathetic vasomotor tone in the collateral arteries, the logical and least harmful method to employ is injection of the appropriate regional sympathetic ganglia. The validity of these theoretical objections to the use of vasodilators is supported by the disappointing results obtained with them in the treatment of acute arterial occlusion (Jacobs, 1959).

ARTERIOSCLEROTIC INTIMAL DISEASE

The circulatory conditions in a limb with a chronic arteriosclerotic occlusion of the main artery are more complex and difficult to assess than those in an embolized limb. In some cases there is no real ischæmia in the resting limb and the effects are limited to functional arterial insufficiency in the muscles during exercise (intermittent claudication). In others there may be local tissue damage or necrosis, often complicated by inflammatory reactions. The theoretical objections which have been advanced against

the use of vasodilators in acute arterial occlusions do not necessarily apply in the case of chronic occlusive disease. Nevertheless, a limb with an occluded main artery presents increased resistance to the inflow of blood and it is not easy to believe that any treatment which causes general vasodilatation elsewhere in the body can possibly increase blood flow into the affected limb. Gillespie (1959) found that, whilst vasodilators will increase blood-flow in healthy limbs, they usually produce a decrease in flow in a limb with an occluded artery.

Clinical trials in patients with chronic occlusive arterial disease have given conflicting results. For example, Goodwin and Kaplan (1951) treated 12 such patients with tolazoline orally and recorded improvement in toe-calf temperature gradient and fluorescein circulation rate at intervals of one to four weeks. Most of their patients also reported subjective improvement. Lynn (1950), using the same drug, could show very little effect on blood-flow in foot or calf in patients with advanced occlusive arterial disease. Edwards and his colleagues (1952) reported improvement in similar patients after intra-arterial injections of vasodilators. Not a few patients suffer unpleasant side-effects from vasodilators, chiefly facial flushing, palpitation, tachycardia and sometimes faintness.

VASOSPASTIC DISORDERS

It is in the vasospastic disorders that most benefit is to be expected from the use of vasodilators, for in these conditions there are small vessels in a state of abnormal constriction. A chemical vasodilator may act directly on these affected vessels and there is no physical obstruction in the main arteries to nullify its effect. Moreover, the patients usually have healthy hearts, able to sustain the increase in output imposed by general vasodilators. Most observers agree in reporting relief of symptoms in a considerable proportion of cases of Raynaud phenomenon (Goodwin and Kaplan, 1951; Lynn, 1950; van Wijk, 1953; Gillhespy, 1956). In the milder cases, without tissue damage, vasodilators will often reduce the frequency and severity of the attacks. In more severe cases with ulceration, scarring or terminal gangrene of the digits, secondary occlusive thrombosis of the digital arteries has already developed and in these cases little benefit can be expected. By the regular use of vasodilators at an earlier stage of the malady, there is some hope of preventing or delaying this disastrous secondary thrombosis and so limiting necrosis. Vasodilators have usually been found ineffective in the type of Raynaud phenomenon associated with scleroderma and other collagen diseases. The less common types of vasospastic disorder, however, such as acrocyanosis, may receive benefit from the use of vasodilators. In chilblains the benefits are not usually very striking, even with full doses.

AVAILABLE VASODILATOR DRUGS

Any attempt to give a full account of the numerous vasodilator drugs now available would be unprofitable. There are two main groups:—

I. Drugs acting directly on smooth muscle, e.g.:—

Papaverine
Nicotinic acid
β-Pyridyl carbinol (nicotinyl alcohol; 'ronicol')
Meso-inositol hexanicotinate ('hexopal')
Trimethyl cyclohexanol mandelate (cyclandelate; 'cyclospasmol')

II. Adrenergic blocking drugs, acting peripherally on vessels, e.g.:—

Benzyl-imidazoline hydrochloride (tolazoline; 'priscol')
Phenoxybenzamine (dibenylene; 'dibenzylene')
Azapetine ('ilidar')
Chlorpromazine ('largactil')
Butyl p-oxyphenylephrine (bamethan; 'vasculit')

Tolazoline is probably as effective as any of the other drugs in this list and is available as tolazoline tablets B.P., 25 mg. It can be given orally in doses of 25 to 75 mg. and intravenously or intra-arterially in doses of 10 to 20 mg. The dosage used in many of the clinical series reported upon has been quite high (150 to 200 mg. daily). A brief experience of this drug will convince anyone that many patients experience unpleasant symptoms from much smaller doses than this. It is wise to begin with 25 mg. twice daily and to increase the dose only very gradually.

SUMMARY

(1) The most effective and convenient vasodilator for the treatment of angina pectoris is nitroglycerin.

(2) In acute ischæmic syndrome due to sudden occlusion of a main limb artery vasodilators are probably harmful.

(3) In chronic occlusive vascular disorders vasodilators are of very doubtful value.

(4) In vasospastic disorders, especially Raynaud phenomenon, vasodilators are often effective in relief of symptoms.

(5) All vasodilator drugs may cause unpleasant side-effects.

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ANTICOAGULANTS IN CARDIOVASCULAR DISEASE

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THE general public has taken to anticoagulant therapy as if it were the most natural thing in the world. The blood becomes thick, the arteries clog up, therefore the blood must be thinned—so the argument runs and the patients assemble for their monthly blood tests, greet old friends, and only leave their medical advisers surprised that they have not yet demanded the formation of their own Anticoagulant Association or Clot Club, where they can have lectures on the Christmas factor or on the training of residents in venepuncture, interspersed with film shows and trips to the Roman Wall. Yet a very great deal is still unknown of the mechanisms of the diseases for which this treatment is given and even of the way treatment works. Still less is there unanimity upon the indications. Indeed, hospital doctors are probably of one mind only in their hopefulness that some day fairly soon the whole elaborate paraphernalia of anticoagulant therapy will be superseded by something both simpler and more effective. That will be the day for the Residents' Party.

THEORETICAL BASIS

Part of the rationale of the treatment is, of course, simple enough. Clotting of blood in the veins of bed-fast legs or in an atrium which has been paralysed, as Sir James Mackenzie put it, by fibrillation, or which is engorged behind a narrowed mitral valve, and thrombus formation on the inner wall of infarcted heart muscle, are dangerous entities easy to understand. But why thrombosis occurs more readily in some people than others, how dietetic factors operate, why females are protected, the part played by cholesterol and lipoproteins, the relationship between thrombus formation and atheroma, the importance of purely mechanical factors such as the way arteries branch—these are matters upon which a great deal of work is being done and to summarize the present state of knowledge is by no means easy.

As in rheumatic fever, genetic factors probably play a part, and the remarkable tendency for several members of a family to develop coronary disease is probably not fully explained on the basis of similar dietary habits. It seems likely that this genetic factor operates through the clotting mechanisms of the circulating blood, though we know so little about the different kinds of endothelium and intima that we may simply be excluding them out of ignorance. The part played by female sex hormones, whereby premenopausal women are immune to coronary disease, is also not fully understood. In fact it is particularly intriguing because they develop plenty of atheroma in the aorta but little in the coronary arteries. The sex hormones influence the cholesterol-phospholipid ratio and the natural production of

heparin by the body's mast cells but how important this is we do not know. Certainly much of the controversy between those who believed dietetic factors to operate through the mechanism of cholesterol deposition in artery walls and those who, with Professor Duguid, believed that atheroma is largely the end-result of thrombus formation, has largely died down.

Since it became clear that most cholesterol-fed animals get plenty of coronary atheroma but no thrombus or infarcts and that in man cholesterol was important mostly through its effect on clotting, the palm of victory has largely passed to Professor Duguid, and it seems likely that a diet rich in saturated fats causes a rise in cholesterol and in the *beta*-lipoprotein to which it is bound, and in doing so increases platelet stickiness and thromboplastin generation and retards fibrinolysis. At this point mechanical factors enter, and platelets, which probably initiate formation of thrombi, settle themselves in certain situations, of which the bifurcation of arteries is one of the most important. Substances therefore which interfere with blood clotting may be expected both to discourage the formation of thrombi in moving blood and of clots in stationary blood and also probably to retard the more subtle processes which we call formation of atheroma. At present such substances are given principally for the former purposes and their value in the latter remains to be assessed.

MECHANISM OF ACTION

Heparin.—This mucopolysaccharide is active against thromboplastin, prothrombin and thrombin itself, and is a powerful anticoagulant, so that new clots will not form and clots already formed will not propagate. It also 'clears' the blood of lipid substances by its action on an enzyme mechanism and this may be of indirect importance in preventing formation of thrombi. It is only active, however, when given parenterally, and there are thus obvious limitations to its long-term use. Indeed, it is so powerful that even if it were possible to use it by mouth or, as has been tried, sublingually, there would be too many hazards from cerebral hæmorrhage and the like for safety. For short-term effects, however—preventing propagation of thrombi, allowing clots once formed to shrink and recanalize, preserving an acutely ischæmic limb until nature or the surgeon has provided an adequate blood supply—it is unsurpassed in usefulness. It has also the great merit that its action can be instantaneously neutralized by injection of protamine sulphate solution, each millilitre of which will take care of 5000 units of heparin. The effect of the protamine may, however, wear off later, and the injection need to be repeated.

There are several long-acting and orally effective anticoagulant substances. *Phenindione* ('dindevan') is probably the most widely used today, but for the odd patient who is allergic to it or in whom phenindione works badly there are several *coumarin derivatives* now available: e.g., phenprocoumon ('marcoumar'), ethyl biscoumacetate ('tromexan'), and nicoumalone ('sinthrone'). They act by preventing formation of prothrombin and the intensity of this action is measured by Quick's one-stage or sometimes two-stage method of

estimating prothrombin time. The result is variously expressed as a percentage of prothrombin activity, or as an index, or almost as simply and equally accurately as a retardation of the clotting process usually to 2 to 2½ times the normal. Their action can be neutralized by the injection of menaphthone (vitamin K) but only after a latent interval of about an hour. These oral anticoagulants also have the demerit that they are slow in attaining their effect and the initial ingested dose does not lower the prothrombin for about thirty-six hours.

TECHNIQUE

Heparin must be given intravenously or intramuscularly. Intravenous dosage is usually easy, causes little discomfort, and its effect is immediate but rather short-lived. Intramuscular injections have a longer action but cause pain and bruising. They should be given deeply and with 2 ml. of 2 per cent. lignocaine added: 5000 units per ml. strength is usually employed and dosage is 10,000 to 15,000 units every six to four hours; 25,000 units intramuscularly every twelve hours is an alternative method apt to be rather more painful. Heparin is an expensive drug likely to cost about 45*s*. a day.

Phenindione is effective by mouth, cheap (2½d. per 50-mg. tablet) and is available in strengths of 50 and 10 mg., the former being the more widely employed. The dosage schedule is 200 mg. the first day, 100 to 150 mg. the second day, and 50 mg. on the morning of the third. Subsequent daily dosage is regulated by prothrombin estimations and varies greatly with different individuals—from 25 to 175 mg. a day. Divided dosage produces a more stable effect. Hypersensitivity to the drug is met with and is much commoner than with heparin but not very often troublesome. The patient should be warned that the drug does impart an orange colour to his urine. Prothrombin estimations must be made to begin with daily, later less often, and patients on long-term therapy can usually be safely controlled with estimations at two- to four-week intervals. The estimations are made on 5-ml. samples of venous blood drawn into a tube of anticoagulant and reported in terms of prothrombin time or index of activity. Usually a prolongation of prothrombin time to between 2 and 2½ times the normal, or a reduction of activity to between 20 and 30 per cent. of the normal is aimed at. The only important complication of therapy is hæmorrhage, hæmaturia being much the commonest, and many physicians instruct the patient to make 'occultests' each day on their urine. When patients on long-term therapy fail to cooperate in attending for their prothrombin estimations their treatment should be discontinued forthwith.

SHORT-TERM THERAPY IN MYOCARDIAL INFARCTION

Treatment by anticoagulants may be broadly divided into short-term and long-term. The former is given for a few weeks to tide a patient over a crisis, the latter for months or years to prevent recurrence of trouble. In either case the most frequent indication is coronary artery thrombosis. In short-term use for this malady the three principal objects are: (1) to prevent extension

of thrombosis, (2) to prevent endocardial thrombosis with attendant risk of systemic embolism, and (3) to prevent phlebothrombosis in the legs with risk of pulmonary embolism.

Myocardial infarction most often results from the sudden occlusion of a major coronary artery by thrombosis in its lumen. Almost certainly the occluded vessel may reopen spontaneously to the passage of blood, just as peripheral arteries such as the popliteal are known to do after thrombosis or embolism. The mechanism is either by retraction of clot or by dissolution of it by fibrinolytic enzymes or by both. There is evidence that such fibrinolytic activity, always present to some extent in the blood, may be much increased when a patient has had a myocardial infarct (personal observations). Such a mechanism would certainly explain some of the cases in which at post-mortem examination infarction is found but no coronary thrombosis. These two mechanisms are much more likely to be effective if the small segment of thrombus which first blocked the vessel can be prevented from extending and this is where anticoagulants have their place.

Secondly, it is a common experience that a considerable proportion of patients who experience a major myocardial infarction either develop it in stages over several days or over a week or two, or else have significant premonitory symptoms over a similar period of time, either in the form of a sudden appearance of angina of effort or in the sudden intensification of that symptom. A man previously well who suddenly finds himself unable to walk more than a hundred yards without getting pain or who gets spontaneous attacks of angina in bed, in both cases relieved by nitroglycerin, should be pictured as having acutely narrowed a coronary artery by thrombus formation or as having wholly occluded it, and a few of them will be shown, by electrocardiogram and/or by the transaminase test, actually to have sustained a small myocardial infarct. A fair proportion of such patients proceed within a week or two to further thrombosis and much more extensive infarction unless they are given anticoagulant therapy. The same is true of a man previously only liable to angina on steep hills who suddenly finds himself unable to walk more than twenty or thirty yards. Similarly, a patient may have a two-hour pain due to a small myocardial infarct one day, the next have a one-hour pain, and two days later develop a twenty-four hour pain due to further massive infarction. Heparin given the first day may well prevent the later extensions. It is in these cases that alertness and promptitude by the general practitioner may be of the greatest service in preventing gross cardiac damage. One must not, of course, expect invariable success. All who have treated cases of myocardial infarction in hospital know that some patients will have further extension despite efficient anticoagulation, and that some patients will die—of ventricular arrest, or ventricular fibrillation, or some other complication—no matter what is done. But they also know that many cases are admitted for treatment unnecessarily late because the patient has insisted that it is only indigestion and the doctor has waited for a fall in blood pressure or has been put off because the pain has responded

to nitroglycerin. The distinction between angina pectoris and coronary thrombosis is a useful one but by no means always clear-cut, and the most healthy attitude is not to ask 'is this ischæmia or infarction?' but rather 'what is happening to the coronary artery of this patient?'.

Endocardial thrombosis is a smaller hazard and easy enough to understand. The subendocardial muscle is farthest from the major coronary arteries and often preferentially infarcted, and then the endothelium is destroyed; exactly why is not clear, for one would expect it to be adequately nourished from heart blood. Clot then forms, and pieces are liable to break off and land in a cerebral, mesenteric, or limb vessel. Such embolism is a serious calamity, for medical treatment is by no means always effective, and a man with a recent myocardial infarct is a poor risk for operation. Anticoagulants will reduce the risk of such embolism most substantially.

The value of anticoagulant therapy in acute myocardial infarction has been attested by a number of controlled clinical trials, the great majority of which have shown that the incidence of thrombo-embolic complications is reduced by 10 to 20 per cent. and mortality by 6 to 10 per cent. The statistics of those who deny the treatment's value are more open to criticism than the figures of those who admit it. The value is greatest in male patients aged 50 to 70 who have large infarcts, and marginal in young patients with small ones. But the partiality that some good-risk patients have for later becoming bad risks is disconcerting, and the selection of good-risk patients who do not need anticoagulants requires a self-confidence in prognosis which better doctors rarely possess.

LONG-TERM THERAPY IN MYOCARDIAL INFARCTION

To continue anticoagulant therapy for months or years is a somewhat arduous procedure only justifiable if it can be shown definitely to reduce mortality or morbidity or both. Obviously it might be expected to prevent recurrence of coronary thrombosis, and if Professor Duguid's theories are correct it could conceivably also retard development of atheroma and hence, worsening of angina. Its usefulness in the former purpose has recently been the subject of a Medical Research Council Trial (*Brit. med. J.*, 1959, **i**, 803). Its value for the latter purpose will be similarly studied very soon.

From the completed trial it has not been possible to prove that long-term therapy is of value in women, but in men the risk of re-infarction is reduced by two-thirds and rather fewer of the treated patients than the controls suffer from angina. The differences apply to all ages up to 70 years but especially to those less than 55 years. The benefit was most impressive during the first three months after primary infarction but apparent up to at least two years.

The case for long-term anticoagulant therapy can therefore be regarded as proved but some discrimination and care are still needed in the selection of patients for it: his temperament, reliability in carrying out instructions, distance from doctor and hospital, and the interference with his work. Age is obviously also a factor, and common sense and kindness would suggest that six months or so may be a reasonable 'long-term' period after infarction for those past the age of 65. Absolute contraindications include active peptic

ulcer, a known bleeding tendency, uncontrolled hypertension, and a history of intra-cerebral or subarachnoid hæmorrhage. It is in any case well to remember that long-term anticoagulant therapy is at best an adjuvant to other and important medical treatment: namely, a low animal fat diet, correction of obesity, reduction of high blood cholesterol, treatment of hypertension and so on.

HOME OR HOSPITAL TREATMENT

The initiation of anticoagulant therapy obviously involves a technique which is difficult to carry out in a patient's home, so that the great majority are admitted to hospital or nursing home. There they often come under the care of consultants, and it is probably for this reason that consultants usually retain the responsibility afterwards when therapy is continued on a long-term basis. Certainly where nursing and laboratory services are readily available to the general practitioner there is no reason why he should not manage the treatment himself, and particularly so when it is of this long-term type.

PERIPHERAL VASCULAR DISEASE

Diseased conditions of the coronary arteries such as have been described are, of course, just part of a general process affecting the whole body, and to a large extent anticoagulants are used on the same principle in the treatment of peripheral vascular disease: that is to say, short-term courses to tide over acute episodes and long-term therapy to prevent recurrence. The peripheral circulation has the great merit, however, that some parts of it are susceptible to direct surgical attack on the obstruction. As a result, removal of emboli and thrombendarterectomy for chronic and lengthy obstructions, and in other instances actual replacement of segments of vessel, are being increasingly used.

In acute occlusion the work of the surgeon may be greatly eased if propagation of clotting can be prevented by prompt administration of anticoagulants, especially heparin, and here the general practitioner has the chief opportunity and responsibility. His duties can be summarized as 'give heparin at once, keep the part cool, and send straight into hospital'. These principles apply whether the cause is thrombosis or embolism, but especially so for the latter where the block is initially of much more limited extent and the prospects of surgical cure are vastly better. The victims are usually suffering from mitral stenosis or atrial fibrillation with or without such stenosis, from subacute bacterial endocarditis, or from recent myocardial infarction, and the primary cause is a most important clue to the diagnosis. The most urgent emboli are the mesenteric, for the prognosis of infarcted gut is very bad. In the limbs, arms usually recover without operation and so do legs if the block is popliteal or lower, but heparin will enhance the chances. Blocks in femorals, iliacs, and aorta, often require surgery, and heparin will greatly prolong the time up to which operation is feasible.

Long-term anticoagulant therapy in peripheral vascular disease is a

matter upon which there is no consensus of opinion. The theoretical basis is sound but the experimental proof of value is difficult to obtain and the practical objections not inconsiderable. The best established indication is probably prevention of recurrent embolism in patients with chronic rheumatic mitral valve disease usually with atrial fibrillation, and a few patients with atrial fibrillation in other forms of heart disease.

PULMONARY EMBOLISM

To prevent pulmonary embolism by preventing or treating clots in the legs is more meritorious than to treat the disaster itself, but it is better to treat the disaster itself than to await a second one. Anticoagulants serve both purposes and are usually given for two to three weeks. If hæmoptysis is severe the heparin is best omitted. The worst cases, however, if they do not die at once, often have no hæmoptysis and should be given heparin immediately.

CEREBRAL VASCULAR DISEASE

Much work, especially in this country, has been done in recent years to establish the place of anticoagulants in vascular disorders of the brain, and it is clear that such therapy has a much more limited role there than elsewhere. Direct surgical attack upon freshly formed cerebral thrombi is not as yet practicable. Much the commonest lesion is thrombosis, but successful treatment by anticoagulants is made hazardous by the fact that even the most brilliant neurologists will erroneously diagnose as thrombosis a number of cases which really have hæmorrhage. Moreoever, the risk of bleeding into an infarct which has originally been caused by thrombosis is very real. It is thought to be a lesser risk in an embolic than in a thrombotic infarct, perhaps because the unaffected vessels are usually healthier. No-one could therefore blame a practitioner who withheld heparin from both.

For the thrombosis which advances in stages or has a fluctuating course, however, the case for anticoagulants is much stronger, but the best case of all, however, is the patient with recurrent cerebral 'spasm', provided this is not part of a hypertensive encephalopathy. These patients have a neurological deficit—hemiplegia, paræsthesia or hemianopia—which lasts some minutes or even an hour or so or, in the case of the retinal artery, monocular blindness for one to three minutes, and it then clears up only to return on several occasions within hours, days, or weeks. Many have a partially or wholly blocked internal carotid artery. Others have basilar or cerebral artery insufficiency. A few require surgical treatment—e.g. for a stenosed internal carotid artery—but most clear up if they are given anticoagulant therapy for some weeks, and a good proportion develop a permanent paralysis or blindness if they are not. The need may be urgent. Most of us would prefer to be allowed to perforate our appendixes unnecessarily than to develop a preventable and irrecoverable hemiplegia.

CARDIOVASCULAR STIMULANTS

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Too often cardiovascular stimulants are used without the proper recognition and treatment of the primary cause of cardiac dysfunction. For example, in severe systemic hypertension the left ventricle is pumping against an increased peripheral vascular resistance that should be lowered by hypotensive therapy. In treating the symptoms of severe aortic stenosis the overburdened left ventricle, whose systolic pressure may be three times normal, can be relieved of its obstruction by aortic valvotomy, without which other measures may fail. When atrial fibrillation is due to thyrotoxicosis, the thyrotoxicosis itself must be treated. In cor pulmonale, secondary to chronic chest disease, treatment of the associated lung infection is essential.

Cardiovascular stimulants can be considered in relation to heart failure, respiratory depression, disorders of cardiac rhythm, and the hypotensive states. Their correct use is in conjunction with appropriate therapy for the underlying cardiac disorder, and such treatment itself often provides the most essential stimulation.

HEART FAILURE

Digitalis is one of the most efficient cardiac stimulants; it appears to act directly on the myocardium, increasing the force of myocardial contraction. Thus digitalis slows the heart, lowers venous pressure, raises blood pressure, and causes a diuresis. Its most important use is in heart failure. A full account of this excellent stimulant is given elsewhere in this symposium (Evans, 1961). Dietary restriction of sodium and venesection both reduce blood volume and lower venous pressure in heart failure, thereby stimulating the heart. Similar effects are obtained by the chlorothiazide group of drugs, which enhance the elimination of sodium from the body, and the important place of the mercurial diuretics is well established. The effects of venesection may be rapidly achieved without blood-letting, by causing venous blood to pool in the periphery. The legs are placed in a dependent position, and tourniquets applied to all four limbs, at a pressure sufficient to stop venous return while allowing arterial inflow. In pulmonary œdema the outpouring of secretions interferes with the passage of oxygen across the alveolar membrane. Oxygen by inhalation can then help to raise the oxygen saturation of the blood towards normal. Early in the sequence of events leading to heart failure, blood flow through the kidney becomes diminished, with consequent sodium retention and other electrolyte changes. Any drug that would selectively increase renal blood flow under these conditions should act as a first-class cardiac stimulant, but none exists at present for clinical use.

RESPIRATORY DEPRESSION

The respiratory centre is often depressed in patients with heart failure, not only due to the disease but often due to treatment with sedatives and hypnotics. Aminophylline is a powerful respiratory stimulant, and can abolish Cheyne-Stokes respiration. A dose of 0.25 to 0.5 g. is given intravenously or intramuscularly and can be repeated. This drug has a widespread action, for it also relieves bronchospasm, lowers venous pressure and increases the cardiac output. Thus pulmonary œdema and dyspnœa are relieved, and diuresis occurs. Nikethamide is an analeptic that stimulates the vital centres. It may be valuable in depression of the respiratory centre by drugs, in cor pulmonale and after massive pulmonary embolism. A dose of 1 to 4 ml. is given intravenously and repeated if necessary. Strychnine also acts by stimulating the respiratory and vasomotor centres, although therapeutically its action is less impressive.

DISORDERS OF CARDIAC RHYTHM

Disorders of cardiac rhythm demand different forms of cardiovascular stimulation. When cardiac standstill or ventricular fibrillation occurs, only immediate stimulation of the heart may save life. Direct stimulation of the heart to reverse ventricular fibrillation, with a powerful electrical shock delivered through electrodes directly to the heart, is commonly performed at the time of thoracotomy for cardiac surgery. Standstill of the heart may occur during anæsthesia and cardiac surgery, and may of course develop spontaneously, as in ischæmic heart disease. In the anæsthetic cases thoracotomy and cardiac massage is accepted treatment. The techniques have been well described, and will not be dealt with here. The indications for such interference in patients with ischæmic heart disease, however, are still greatly disputed. If thoracotomy is not to be performed, thumping of the chest over the heart may stimulate the return of normal beating, and the intracardiac injection of adrenaline, which stimulates the nerve endings in the myocardium, can do the same. In other patients thoracotomy and cardiac massage may lead to an uninterrupted recovery and many years of health. Full discussion of which patients with this mortal disease should be subjected to these manœuvres would be out of place here. Cardiac massage may be correct in a young man recovering from a first attack of cardiac infarction; whether it is so in an older patient with an extensively damaged myocardium seems doubtful.

In complete heart block ephedrine, ½ to 1 grain (30 to 60 mg.) thrice daily, tends to increase the ventricular rate and is very efficient in preventing faintness and syncope, but in severe cases the subcutaneous injection of 0.5 ml. of a 1:1000 solution of adrenaline may be needed. Cortisone derivatives may sometimes abolish heart block, and this therapy is still under investigation. When these measures fail the use of internal electrical artificial pacemakers to stimulate the heart in patients with incapacitating heart block is proving increasingly worth while. When undue bradycardia occurs due to

digitalis overdosage the drug must be temporarily withheld; if other action is needed atropine will counteract the vagal effects of digitalis.

HYPOTENSIVE STATES

Hypotension, such as can occur after cardiac infarction, may need urgent treatment. In hospital the most satisfactory of the pressor drugs is noradrenaline, given by a slow intravenous drip. By increasing the peripheral vascular resistance and improving myocardial contractility, it raises the blood pressure and improves coronary and renal perfusion. The blood pressure, however, must not be allowed to rise too high, or the added load on the left ventricle can precipitate left ventricular failure. Intravenous drips are not always practical in the patient's home, and mephentermine sulphate and metaraminol hydrogen tartrate are effective pressor agents that can be given by injection. Metaraminol has the advantage that it is less likely to cause tachycardia. Repeated injections are required to maintain the blood pressure.

CONCLUSION

It must be stressed that cardiovascular stimulants should not be used indiscriminately, but with full regard to the primary cause of cardiac dysfunction, and together with other appropriate therapy.

SUMMARY

The importance of using cardiovascular stimulants in conjunction with the correct treatment of the primary cause of cardiac dysfunction is stressed. Cardiovascular stimulants are considered in relation to heart failure, respiratory depression, disorders of cardiac rhythm and the hypotensive states.

In heart failure the use of digitalis, sodium restriction, venesection, and oxygen is noted.

The importance of aminophylline and nikethamide in respiratory depression is discussed.

With ventricular fibrillation and cardiac standstill various measures, including electrical and mechanical stimulation of the heart, may be needed.

Complete heart block may be treated with ephedrine, adrenaline, cortisone derivatives and an artificial pacemaker.

In the hypotensive states different pressor agents may be used to maintain the blood pressure.

Reference

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ANTIBIOTICS IN CARDIOVASCULAR DISEASE

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THE major triumph of antibiotic therapy in cardiovascular disease has been the successful treatment of bacterial endocarditis, previously an almost uniformly fatal illness, but useful contributions have been made to the prophylaxis of acute rheumatism, and the treatment of pyogenic and tuberculous pericarditis and cardiovascular syphilis. Apart from these obvious benefits, antibiotics have saved many lives by arresting the bronchopneumonia which is such a common terminal event in cardiac failure, and they play an essential part in the treatment of the infection which usually precipitates respiratory and so cardiac breakdown in chronic cor pulmonale.

It will be convenient to deal with the more direct uses of antibiotics in cardiovascular disease in the order of their importance.

BACTERIAL ENDOCARDITIS

There are still no grounds for complacency over the results of treatment of bacterial endocarditis. The acute form is not often diagnosed during life and the mortality rate remains between 50 and 75 per cent. Subacute bacterial endocarditis carries an immediate mortality of 25 to 35 per cent. (Cates and Christie, 1951; Morgan and Bland, 1959) and a substantial proportion of the survivors are cardiac cripples. Understanding of the use of antibiotics in the treatment of bacterial endocarditis demands an appreciation of the pathological basis of the problem. The organisms are enmeshed in a mass of fibrin and platelets which is avascular and are therefore protected from both cellular and humoral mechanisms of defence. It follows that an effective antibiotic must be capable of ready penetration into the affected area and should be bactericidal rather than bacteriostatic. Penicillin and streptomycin are therefore the most useful antibiotics and the tetracyclines are the least successful. Since a considerable gradient of concentration is likely to exist between blood stream and the depths of the lesion, blood levels must be reached which are several times greater than the bactericidal level *in vitro*.

Satisfactory treatment depends on successful identification of the organism and determination of its antibiotic sensitivity. Treatment should not be delayed needlessly while awaiting the results of culture, for most investigators (e.g. Dormer, 1958; Barritt and Gillespie, 1960) are of the opinion that positive cultures are usually obtainable at the first attempt, and are rare after the third. Both aerobic and anaerobic cultures should be made and six cultures may well be spread equally over forty-eight hours. It is often necessary to wait for several days for a positive culture if antibiotics have

recently been given and in these circumstances treatment may properly be delayed. Ten to fifteen per cent. of patients with bacterial endocarditis have persistent negative blood cultures.

Although many of the clinical features of acute and subacute bacterial endocarditis are distinct, a bacteriological classification is essential for therapy.

Streptococcus viridans.—The Medical Research Council's report (Christie, 1948) established that 2 mega units of penicillin daily for four to six weeks in three-hourly doses was a minimum for sensitive infections and its recommendations rest on a more firmly established basis than subsequent modifications. There is, however, fairly general agreement that 1 mega unit six-hourly for the same period is more tolerable to the patient and equally effective. Benzylpenicillin is probably the best preparation, as higher peak levels are attainable. Penicillin alone in the above dosage should be used only if the organism is sensitive to 0.1 to 0.2 unit/ml., and an additional mega unit of penicillin a day must be added for each 0.1 unit/ml. decrease in sensitivity. Doses of penicillin greater than 10 mega units a day are difficult to maintain for long periods and the dose of penicillin may be halved if 0.5 g. of probenecid is given six-hourly. Larger doses of penicillin may be given intravenously through an indwelling needle. Streptomycin appears to have a powerful synergistic effect and if the organism is resistant to more than 1 unit of penicillin/ml., 0.5 to 1 g. of streptomycin twice a day should be given. The smaller dose should be given in patients over 60 owing to the great risk of disabling vestibular damage.

Successful results with procaine penicillin (Roston and Stollerman, 1949), 0.6 mega unit twice daily, and with oral phenoxymethylpenicillin, 1 to 2 mega units four-hourly (Quinn *et al.*, 1956), have been claimed (and the new synthetic penicillin, phenethicillin, may prove useful). Two-week courses of treatment with penicillin, probenecid and streptomycin have also been successful. Such modifications are best reserved for those unable to endure conventional treatment and, even in these, to patients with organisms sensitive to less than 0.1 unit/ml. Bacterial endocarditis is not a condition in which effective therapy should be rashly abandoned.

Streptococcus fæcalis.—Infections with this organism have proved difficult to control and conclusions based on *in vitro* sensitivity are often misleading. Hunter (1946) showed the value of a combination of streptomycin and penicillin against these organisms. Penicillin, 20 mega units daily given in divided doses four-hourly through an indwelling cannula, combined if necessary with streptomycin, 2 g. daily, and probenecid, 0.5 g. six-hourly, may be regarded as standard treatment (Dormer, 1960). Failure to respond may necessitate much larger doses of penicillin—up to 100 mega units daily—or novobiocin, vancomycin or ristocetin may be used.

Staphylococcus.—Staphylococcal endocarditis has become an important complication of operations, including those on the heart itself, and the mortality remains high. Sensitive strains may respond to penicillin alone,

combined with probenecid, but a combination with streptomycin, as for *Streptococcus fæcalis*, is usually wise from the start. Additions of chloramphenicol, erythromycin, novobiocin, vancomycin or ristocetin may be necessary. It seems possible that the use of the newer penicillins resistant to penicillinase will help to solve this difficult problem.

Other organisms.—Recommendations for treatment may be found in the reviews of Dormer (1960) and Tumulty (1960).

The bacteriologically negative case.—Some of these cases are due to fungal or Rickettsial infections, but these are a minority. A wise procedure is to use the combination of penicillin, streptomycin and probenecid recommended for *Streptococcus fæcalis* until the failure of clinical response shows this to be inadequate. Modification of the programme becomes a matter of trial and error and it is not surprising that the mortality is high.

Blood cultures usually become negative soon after treatment is started, but, unfortunately, there is no single guide to adequate therapy, which often has to be assessed on the clinical response, as shown by fall in temperature, disappearance of sweating and anæmia and the change in the general appearance of the patient. Minor embolism may persist for some time and splinter hæmorrhages indefinitely. The latter are not uncommon in normal people and have been reported as occurring in 44 per cent. of patients with mitral stenosis (Platts and Greaves, 1958). A fall in the sedimentation rate is often delayed well into convalescence.

Pyrexia may be due to the antibiotic itself or to complications such as thrombophlebitis, secondary infection or muscle necrosis at the site of injection. Precipitate changes in treatment should be avoided.

PROPHYLAXIS OF BACTERIAL ENDOCARDITIS

Adequate prophylaxis of bacterial endocarditis in those at risk is still a neglected measure. Although the probability of infection varies in different types of congenital and rheumatic heart lesions, antibiotic cover should be given to all patients in the circumstances discussed below. It is important to remember that even today the assessment of the significance of systolic murmurs is not completely accurate and that if any doubt exists an antibiotic should be given. There is an appreciable incidence of bacterial endocarditis in patients thought to have benign systolic murmurs. Long-term antibiotic prophylaxis on the lines so successful in acute rheumatism is not practicable in bacterial endocarditis for the organisms are in situations in which complete elimination is impossible and many are capable of developing antibiotic resistance.

Dental extraction remains the commonest cause of infection but it is also liable to follow operations on the urinary tract such as cystoscopy and prostatectomy, and operations on the alimentary tract, especially hæmorrhoidectomy, and childbirth. It is wisest to give prophylactic antibiotics before any operation. Prophylactic antibiotics act mainly by preventing implantation rather than postoperative bacteriæmia and the maximum con-

centrations should be achieved soon after the operation. It has been suggested that prolonged preoperative treatment may increase the danger of antibiotic resistance.

The evidence for the value of the very varied regimes suggested by various authorities is inconclusive. Hobson and Juel-Jensen (1956) suggest 1 mega unit of penicillin thirty minutes before operation, followed by 1 mega unit on the same night, repeated on the morning and evening of the following day. After extensive extractions this dosage is continued for several days. Erythromycin may be used if serious penicillin sensitivity is present. Tetracycline has been recommended when operations on the urinary tract are carried out (Tumulty, 1960) but, since *Streptococcus fæcalis* is the most likely invader, penicillin is probably still the drug of choice.

The prophylaxis of bacterial endocarditis is likely to be efficient when the care of the patient is properly organized by the family doctor, but is likely to break down in a shifting population relying too much on hospital care.

RHEUMATIC HEART DISEASE

The main role of antibiotics in the treatment of rheumatic heart disease lies in the prevention of further attacks, but Mortimer and his colleagues (1959) have produced evidence that the incidence of valvular heart disease one year after an attack of acute rheumatic fever is reduced if penicillin is given in doses designed to eliminate the streptococcus for six weeks at the beginning of the illness. The dosage used was benzylpenicillin, 0.5 mega unit four-hourly for ten days, procaine penicillin, 600,000 units twice daily for eleven days, and a dose of 1.2 mega units of benzathine penicillin on the 22nd day.

Bactericidal doses of penicillin should be given to patients who have had an attack of acute rheumatism in any of its forms, when they develop an infection with a Group A β-hæmolytic streptococcus. Long-term prophylaxis may be achieved by oral benzylpenicillin, 0.2 mega unit twice daily or phenoxymethylpenicillin, 120 mg. twice daily, or 1.5 mega units of benzathine penicillin can be given intramuscularly once a month if there is any doubt of the patient's cooperation. Prophylaxis should be continued until adult life is reached and be resumed if special risks occur, as in army camps and hospitals. A reduction in the recurrence rate to about a fifth of the control level can be expected.

PERICARDITIS

Pyogenic pericarditis is most commonly caused by the pneumococcus but may be produced by other organisms especially the streptococcus and staphylococcus. (Diagnostic aspiration is of course desirable to establish the nature of the infecting organism.) A dose of 1 mega unit of benzylpenicillin intramuscularly every six hours is sufficient to control infections with sensitive organisms and may be reinforced by instillation of 1 mega unit into the sac when aspiration is performed. Surgical drainage is seldom necessary unless the organism is resistant or treatment has been unduly delayed.

Tuberculous pericarditis is declining in frequency like other forms of tuberculosis. Treatment should be started with streptomycin, 1 g. intramuscularly, combined with isoniazid, 200 mg. daily, and sodium PAS, 5 g. three times daily. In view of the risk of vestibular disturbance streptomycin may be reduced to 1 g. three times weekly if the patient is over 40. Once the drug sensitivity of the organism has been determined treatment with two effective drugs is continued for at least twelve months. Early treatment is essential if chronic constrictive pericarditis is to be prevented.

SYPHILITIC AORTITIS

It has been customary until comparatively recently to start treatment with bismuth and iodides for fear of inducing a Herxheimer reaction if an arsenical preparation or penicillin is used to initiate treatment, but the occurrence of such reactions in cardiovascular syphilis is extremely doubtful. Most clinics now prefer to treat with penicillin from the start. A suitable course is 0.6 mega unit of procaine penicillin daily for ten days, and it is probably wise for the patient to rest in bed during the initial course of treatment.

Serological reversal is unusual in aortic syphilis but a normal erythrocyte sedimentation rate is unusual if aortitis is still active. It is usually wise to give two or three further courses of penicillin at six-monthly intervals, and many physicians still prefer to give a course of bismuth after the initial penicillin course. The evidence that penicillin alone is adequate treatment for cardiovascular syphilis is in fact incomplete, and its use rests largely upon indirect evidence and on its safety and convenience. Leonard and Smith (1957) found that the results of treatment in syphilitic aortic regurgitation were less satisfactory than in those fully treated with arsenic and bismuth, though better than in untreated cases, but their series included only a relatively small number of patients, and further study is clearly desirable.

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SEDATIVES AND ANALGESICS IN CARDIOVASCULAR DISEASE

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Analgesics and sedatives are important and, at times, essential parts of treatment but their use is empirical and symptomatic and they are but a last line of retreat for the physician.

PALPITATIONS

Tachycardia of effort is a common complaint of the over-anxious and the patient with mild hyperthyroidism, and is often met with in patients convalescing from acute infections when, I believe, it is much more often due to mild and transient hyperthyroidism than to myocardial damage. Assurance of the comparative insignificance and the transient nature of the symptoms is generally all that is necessary, but I have found quinine hydrobromide, 3 grains (200 mg.) thrice daily, to be a useful sedative in the more severe cases, prescribed as follows:—

Quinine hydrobromide B.P.C. 1949	120 minims (8 ml.)
Dilute hydrobromic acid B.P.C. 1949	360 minims (24 ml.)
Water	to 6 fluid ounces (170 ml.)

60 to 120 minims (4 to 8 ml.) thrice daily

Frequent *extrasystoles* may occur in the absence of any cardiovascular lesion. They can be a source of considerable apprehension and a cause of sleeplessness. Explanatory reassurance is the main line of treatment but if sedation is also required a tablet of phenobarbitone, $\frac{1}{3}$ grain (20 mg.), and belladonna, $\frac{1}{4}$ grain (15 mg.), can be tried—the euphoric and anti-vagal actions of belladonna seem to enhance the sedative action of phenobarbitone and are particularly helpful when there is an associated acid dyspepsia.

I have found the milder tranquillizers (e.g. meprobamate) of very little value in patients with cardiac symptoms related to an anxiety state; if a change from a barbiturate seems desirable, thalidomide, 50 mg. thrice daily, is useful.

ANGINA PECTORIS

For the relief of the acute anginal attack, glyceryl trinitrate remains the drug of choice. It is quickly absorbed from the oral mucosa and, within two minutes, begins to exert its effect as a coronary dilator. Glyceryl trinitrate tablets slowly become inert especially if exposed to air, and preparations such as 'angised' and 'nitrocine' are said to be more stable. Tablets are now made with mannitol instead of chocolate as a basis. Glyceryl trinitrate is a valuable prophylactic, and if taken before exertion or any other circumstance which, from past experience, the patient knows is likely to bring on pain, he may be able to lead a fuller life in comparative comfort. The usual dose

prescribed is 1/100 or 1/130 of a grain (0.6 or 0.5 mg.) but I find that 1/200 grain (0.3 mg.) generally suffices. The main side-effect of glyceryl trinitrate is throbbing headache but this is seldom so severe or prolonged as to preclude its use. If in a case of angina of effort, glyceryl trinitrate appears to be ineffective it is essential to try a known fresh batch of tablets and to check that it is being properly administered before concluding that there is no response to the drug.

Amyl nitrite acts in similar fashion to glyceryl trinitrate. It is inhaled, and exerts its action even more quickly but is less useful because of its disturbing side-effects—flushing, headache and faintness—and some patients feel that the method of administration is too conspicuous.

As glyceryl trinitrate is the most effective coronary dilator, efforts have been made to prolong its action. In one such preparation ('sustac'), glyceryl trinitrate is slowly released from a single tablet as it is digested in the small intestine. Unfortunately, it is difficult to achieve sufficiently rapid absorption of the active drug to maintain its efficacy, as metabolic breakdown is rapid. Pentaerythritol tetranitrate is not so closely related chemically to glyceryl trinitrate but it possesses the property of slow release of the nitrite ion for long periods. Reports of its efficacy vary from improvement in 80 per cent. of patients with angina to no statistically significant improvement.

So far as I am aware, there is no completely satisfactory long-acting drug for the relief of angina pectoris. Many are in use and the evidence from clinical trials regarding their effectiveness is conflicting, which is to be expected when assessment is mainly dependent on clinical impressions and subjective responses. Among those in use are aminophylline and its derivatives, drugs related to glyceryl trinitrate and the amino-oxidase inhibitors. Aminophylline is a coronary dilator but in therapeutic dosage it causes gastro-intestinal upset. 'Theodrox' (aminophylline with aluminium hydroxide), choline theophyllinate and 'etophylate' are better tolerated but have only a minor role in the management of angina pectoris.

Iproniazid, a derivative of isoniazid and a mono-aminoxidase inhibitor, was introduced in the treatment of angina in 1957. It was believed to act by some means other than by coronary vasodilatation. Early favourable results, particularly in severe cases, have not been confirmed and its toxicity is considerable. More recent drugs in this group are nialamide, pheniprazine and 'tersavid'. As yet it is too early to assess their value.

Sulphonylurea derivatives have also recently achieved recognition for their effect in relieving symptoms of angina (and peripheral vascular disease).

CARDIAC INFARCTION

The classical picture of cardiac infarction is of a patient shocked and suffering severe constricting chest pain. In these circumstances, morphine is essential. A dose of ¼ grain (15 mg.) subcutaneously may bring relief but it may be necessary to repeat it within fifteen to thirty minutes. If pain is excruciating, quick relief sometimes follows the slow intravenous injection of

$\frac{1}{8}$ grain (7.5 mg.) of morphine. In my experience there is a tendency to be over-zealous in the use of morphine. It often causes nausea and vomiting and these can be disturbing symptoms in a patient with cardiac infarction. Occasionally a patient's collapse may be precipitated or aggravated by overdosage of morphine, and its use should be restricted to those in severe pain or when shock is associated with pain. Many patients obtain relief from pethidine, 50 to 100 mg., a dose which can be repeated in thirty minutes if pain persists. One has the impression that vomiting and respiratory depression are less common with pethidine than with morphine.

Patients who are given heparin intravenously often state that pain has gone or been greatly relieved after the injection. The exact mechanism of this analgesic action is not known.

Glyceryl trinitrate is by classical teaching contraindicated in the early stages of cardiac infarction, although the onset in some cases is accompanied by a sharp rise in blood pressure. It can be of considerable value in relieving or preventing anginal pain during convalescence, particularly the pain which tends to come when wakening in the morning, or during meals. Nausea and vomiting are often quickly relieved by the intramuscular injection of chlorpromazine, 25 to 50 mg., and in the agitated patient chlorpromazine may be a useful addition to the sedation.

It is often forgotten, particularly after the first few hours of the emergency, that the patient with cardiac infarction may be continuously apprehensive until clinical improvement is obvious. Small doses of phenobarbitone in the daytime and a hypnotic at night are usually desirable, and for the first few nights an opium derivative, e.g. papaveretum ('omnopon') $\frac{1}{3}$ grain (20 mg.) either orally or by injection, can justifiably be added to the hypnotic. Any of the medium- or short-acting barbiturates can be used, and chloral hydrate and thalidomide are available as non-barbiturate alternatives.

It adds greatly to the confidence of the patient who has had a number of attacks of cardiac pain at rest, if he can have available a few tablets of glyceryl trinitrate and one or two tablets of pethidine (50 mg.), the latter to be used only if there is no rapid relief from the former.

ACUTE LEFT VENTRICULAR FAILURE

In the treatment of this acute emergency, morphine is still the drug of choice, and $\frac{1}{4}$ grain (15 mg.) subcutaneously often brings quick relief and restful sleep. I find it helpful to combine this with aminophylline, 0.25 mg. in 10 ml. intravenously, which helps to relieve bronchial spasm and is useful as a diuretic. In the elderly hypertensive, subject to frequent attacks, 15 minims (1 ml.) of 'nepenthe' at night are often of great value in preventing attacks.

In the long-term care of this group of patients, relief from pulmonary congestion by the judicious use of digitalis and chlorothiazide diuretics is often as important as sedatives in ensuring sleep. Although it is always desirable after a time to try to move off the 'scheduled' group of sedatives, it will be found not rarely by trial and error that opium derivatives may be without equal in this circumstance.

CONGESTIVE CARDIAC FAILURE

The value of rest in the treatment of cardiac failure cannot be overestimated but enforced idleness is not always conducive to peace of mind, and rest in bed will be of little avail if the patient is apprehensive, excitable, and restless. Sedatives may then prove a valuable addition to therapy.

For sedation by day, phenobarbitone is often used successfully and its disadvantages are few. By contrast, the use of shorter-acting barbiturates at night has important drawbacks in certain patients. Sometimes transient disorientation is produced, particularly in the elderly, and the associated physical exertion which accompanies this is an obvious danger. It must also be remembered that impaired liver function may be present in congestive cardiac failure, and metabolism of the shorter-acting barbiturates is impaired. For these reasons the non-barbiturate sedatives have an important place, causing less confusion and hangover in the morning. There are several which are both safe and effective, including chloral hydrate, carbromal, glutethimide and thalidomide. My preference is for thalidomide, 100 mg.

Cardiac failure may, by itself, produce mental confusion due to cerebral anoxia and this is often worse at night. Oxygen therapy sometimes affords considerable benefit but, if restlessness and confusion are very severe, it may be necessary to give paraldehyde, 5 to 10 ml. intramuscularly.

HYPERTENSION

Many of the symptoms ascribed to hypertension are manifestations of anxiety and hypertensive patients often show increased cardiovascular response to anxiety. The reduction of mental stresses and strains is an important part of therapy. Sometimes sedatives can help in the control of hypertension, especially in the less severe cases. They may also be used to enhance the action of specific antihypertensive drugs in severe hypertension. Among the barbiturates, phenobarbitone and amylobarbitone are particularly useful. The Rauwolfia drugs have had quite a vogue but their popularity seems to be waning. They usually have a sedative and mild antihypertensive action. Side-effects are, at times, very disturbing, some of these being 'nasal stuffiness', depression, sleeplessness and nightmares.

PERIPHERAL VASCULAR DISEASE

There is considerable divergence of medical opinion on the value of the various vasodilator drugs for the relief of the pain of claudication. There are two theoretical reasons for their ineffectiveness: (1) All peripheral vessels are equally relaxed by the drugs. This leads to a general fall in peripheral resistance and thus to a selective reduction in the blood flow through the ischæmic part. (2) Their chief action is to increase blood flow in skin rather than blood flow in muscle. Nevertheless, some physicians believe that there is clinical evidence of their beneficial actions. Three of the best known are tolazoline, phenoxybenzamine, and nicotinyl alcohol.

THE RAUWOLFIA ALKALOIDS IN THE MANAGEMENT OF HYPERTENSION

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RAUWOLFIA is the drug most often prescribed for hypertension. The reasons are two: it is alleged to lower the blood pressure, although actually its hypotensive action is weak and variable, and it is a tranquillizer to both patient and physician. The chief effect of Rauwolfia is psychological. The patient's blood-pressure anxiety is pharmacologically relieved and he knows he is getting a blood-pressure-lowering drug. The doctor is pleased that his patient is less anxious and is satisfied that he has prescribed for high blood pressure. The faith on both sides, as well as the pharmacological action, may cause neglect of four factors to which every hypertensive patient is entitled: a search for evidence of some secondary form of hypertension, particularly a curable one; practical psychotherapy rather than pharmacological restraint of the psyche; diet, and the benefit of drugs that have fewer side-effects and are less expensive than Rauwolfia.

PRE-DRUG THERAPY

Diagnosis precedes treatment. In patients with hypertension, one must search for a specific cause of the disease, in the hope that it may be one of the few curable types. Further, the physician must decide whether or not the level of blood pressure found at the moment is abnormally elevated. This he will do on criteria of his own or of others, taking into consideration factors such as the sex and age of the individual patient.

When specific causes of hypertension have been excluded and its actual presence has been determined and its degree of severity estimated, there are two forms of treatment that precede or accompany drug treatment. The more important of these is the physician's practical *psychotherapy:* the wisdom, charity, encouragement and guidance that he can give in the art of living. This psychotherapy of which he may often be unaware may be raised to an organized conscious technique within his proper role and competence (Palmer, 1960). When it is an integral part of each patient's examination, it becomes psychological asepsis preventing or reducing high blood-pressure anxiety. Symptomatic relief is obtained by this alone, and the blood-pressure levels of patients with mild and moderate degrees of hypertension are usually modified favourably: sometimes, though rarely, to normal limits.

The second form of treatment preceding or accompanying the use of drugs is *diet.* Reduction of salt, amply proved in the last forty years, lowers the blood pressure and reduces the amount of hypotensive medication required to obtain normal or near-normal limits. Patients with continued

hypertension differ from those with normal pressures in two important respects. Life is shortened for the hypertensive patient due in 75 to 90 per cent. of the cases to accelerated vascular ageing as compared with a 50 per cent. expectancy of this ending for the general population in the United States. Although there are many causes of atherosclerosis, the weight of evidence indicts overweight and animal fats as important participating causes (Palmer, 1959). Therefore, animal fat is reduced as well as salt (200 to 500 mg.), allowing about 900 to 1000 calories in the overweight patient. When ideal weight is achieved, or for the infrequent new patient at ideal weight, carbohydrates and unsaturated fats are added to maintain weight.

I prescribe a low-sodium non-reducing diet in about one-fifth of the mild or moderate (grade I and II) hypertensive patients whom I see. Approximately one-fifth of these show a fall of blood pressure to normal or near normal. In severe benign (grade III) hypertension and all overweight and mild or moderate hypertensive patients I prescribe the low-fat, low-sodium 900 to 1000 carlorie diet. This diet is prescribed for about one-half of office patients with hypertension. One-third achieve normal or near-normal blood pressure, but only 15 per cent. of these require no hypotensive drugs.

DRUGS TO USE BEFORE PRESCRIBING RAUWOLFIA

The hypotensive effect of phenobarbitone, 15 to 30 mg. four times daily, is in my experience and that of others as effective (Smith, 1957) or almost as effective (Shapiro, 1957) in lowering the blood pressure as Rauwolfia, is much cheaper and has far fewer side-effects. Many overweight patients with hypertension have the windy melancholy. Atropine may be combined with the phenobarbitone. My prescription is:—

Sodium phenobarbitone	0.5 g.
Tincture of belladonna	15.0 ml.
Peppermint water	250.0 ml.

One or two teaspoonfuls thrice daily before meals and at bedtime

When lack of energy, disenchantment, discouragement or depression are prominent, or when assistance in reducing calories is necessary by curbing the appetite, my prescription is:—

Elixir of dexamphetamine (1 mg. per ml.)	110 ml.
Tincture of belladonna	15 ml.
Elixir of phenobarbitone B.P.C.	125 ml.

One or two teaspoonfuls thrice daily until 16.00 hours

Diphenhydramine, 25 mg., is ordered at bedtime and repeated twice at any interval for sleep. This antihistaminic is helpful in relieving morning headache, is an effective aid to sleep and rarely causes per-

sistent morning sedation. When morning headache is not relieved, the head of the bed is elevated 4 to 6 inches (10 to 15 cm.) on wooden blocks. This may relieve morning or 'head-down' headache without the use of any drug.

Such medication, combined with practical psychotherapy, and a low-fat and low-salt diet, brings symptomatic relief and some blood pressure reduction in most mild (grade I) and moderate (grade II) cases. These degrees represent the majority of patients seen in routine medical practice. When the blood pressure is not reduced and when salt restriction is not tolerated, chlorothiazide and its derivatives are prescribed before Rauwolfia. Patients with actual or threatened stroke, with angina pectoris and especially those with congestive heart failure, and patients with malignant (grade IV) hypertension require chlorothiazide or its derivatives or mercurial diuretics and ganglionic or sympathetic blockade. Chemotherapy for renal-tract infection and attention to prostatic obstruction in males in middle years and later may be required. The indication for the use of Rauwolfia is in these severe benign or malignant hypertensive patients for its tranquillizing, rather than its weak hypotensive, effect, to render more acceptable the rigors of full drug treatment and the ominous symptoms of vital function failure.

THE USE OF RAUWOLFIA IN PATIENTS WITH HYPERTENSION

There are about three dozen Rauwolfia alkaloids, of which four—reserpine, deserpidine, rescinnamine, and syrosingopine—are clinically used as hypotensive agents, as well as the whole root of *Rauwolfia serpentina* and the alseroxylon fraction. The American Medical Association's 'New and Non-Official Drugs for 1960' lists six drugs and sixteen commercial trade-named preparations. There are also numerous commercial combinations of the Rauwolfia drugs with various sedatives and other additional hypotensive agents, nitrates, or other alleged vascular dilators, and vitamins, some of them containing as many as five different drugs. I stopped listing the preparations three years ago when my count was sixty-nine. The hypotensive action and side-effects of the whole root, the alseroxylon fraction and the four clinically used pure alkaloids vary slightly. The basic pharmacology is the same and is described for reserpine—the longest known pure fraction. What is said may be applied with minor clinical variations to other alkaloids and the whole root. The name 'Rauwolfia' is used for the whole group. The studies on reserpine are taken as guides to the clinical use of all.

Rauwolfia apparently depletes tissue stores of serotonin and also catechol amines. There is evidence that serotonin is important in cerebral function although its precise role is not known (Sjoerdsma, 1959). Clinically the most important action is not its weak hypotensive one, but its tranquillizing one which may be devastating, producing severe prolonged depression

sometimes requiring electroshock treatment. Happily, this is rare and therefore less important than mild suppression of mental alertness, which, in my experience, is quite common and may be very serious in brain workers.

A medical research director with hypertension, coronary heart disease, and congestive failure had a lower pressure and some symptomatic relief while taking Rauwolfia, but preferred the hazards of increased blood pressure to reduced intellectual function.

An engineer with mild, grade I hypertension experienced mild depression on whole Rauwolfia (50 to 100 mg. daily) while the blood-pressure level was controlled at normal or near-normal levels. He became alcoholic, to which he previously tended, and lost his position. Rauwolfia was considered a participating factor in this train of events.

An architect, a scholarly bookseller, a professor, and a florist though manifesting hypotensive responses to Rauwolfia, were all aware of diminished intellectual capacity.

It is therefore my practice to omit Rauwolfia at intervals to discover the subjective mental reaction of patients, especially those with mild grade I or moderate grade II hypertension. Quite often there is a notable brightening of general mental outlook and improved intellectual function. Consequently these patients are more willing to follow salt and fat restriction to control the blood-pressure level. When the latter is not controlled, chlorothiazide or its derivatives are used. When the whole Rauwolfia is used the maximum continued dose should be 100 mg., of reserpine 0.25 mg., of syrosingopine 2 mg.

The mild mental depression or diminished alertness and the slight hypotensive action, together with other side-effects to be mentioned, are contraindications to the use of Rauwolfia in mild and moderate hypertension. On the other hand, in severe benign (grade III) hypertension and in malignant (grade IV) hypertension with distressing symptoms, and the unpleasant effects of ganglionic blockade and other drugs, and restriction in diet, the tranquillizing property of Rauwolfia is its most useful one. Since it depletes pressor amines in blood vessel walls, it may be helpful in angina pectoris and peripheral vascular disease. Indeed, this peripheral blood vessel action may be the mechanism of its mildly hypotensive effect.

In my experience, peptic ulcer has been reactivated by moderate doses of reserpine in one case of grade III severe benign hypertension, promptly clearing on omission of the drug and the administration of an appropriate diet and atropine.

Two patients with very high levels of blood pressure, over-enthusiastically treated by other physicians with large doses of reserpine, 1 mg. intramuscularly every day, experienced falls of blood pressure to normal or near-normal levels, accompanied by a peptic ulcer, one of them with bleeding.

This complication of Rauwolfia is due to increase of gastric secretion, which is the probable cause also of the increased appetite and weight gain

occasionally noticed. Accentuated appetite and large food intake may account for the seeming tendency to salt retention that has been reported.

Patients taking Rauwolfia too often have unexplained bleeding.

A patient on alseroxylon for many months developed a severe hæmatoma after removal of a hydrocele, accompanied by unexplained gastro-intestinal bleeding.

Such episodes may be clinical expressions of depleted vasoconstrictor amines in minute blood vessel walls, and diminished platelet serotonin.

SUMMARY

Rauwolfia and its alseroxylon fraction or one of its alkaloids are alleged to be the first choices in drug treatment of hypertension. Although this is common practice, I disagree for these reasons.

Rauwolfia and its derivatives are weakly hypotensive, but powerfully tranquillizing, diminishing alertness and intellectual function. The latter is far more serious in brain workers because far more common than the occasional serious depression, peptic ulcer, weight gain, salt retention, or unexpected bleeding.

Whereas tranquillization of the patient brings improvement in symptoms or relative indifference to them and to the existence of hypertension and its probable consequences, it may also lull the prescriber to indifferent search for curable secondary hypertension and to neglect of dietary treatment and of psychotherapy—that charm of which Socrates spoke, when, pretending to be a physician, he treated brilliant young Charmides' morning headaches, which doubtless were hypertensive.

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GANGLION-BLOCKING DRUGS IN THE MANAGEMENT OF HYPERTENSION

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Since the introduction in 1948 of ganglion-blocking drugs for the treatment of hypertension, many related substances have been produced and tested but only a few are widely used. On the whole, there has been a steady improvement as regards potency, completeness of absorption and smoothness of action and all the new preparations are effective by mouth. The desired effect of reducing blood pressure through decreasing vasomotor tone is achieved by blocking sympathetic nerve impulses but all members of this group share the disadvantage of concomitant parasympathetic blockade with resultant undesirable side-effects.

Despite the hopes raised by the introduction of drugs which have a selective action in the sympathetic nervous system, such as bretylium and guanethidine, it must be said that there are considerable difficulties in the administration of these compounds largely on account of tolerance and side-effects. At present, at least for patients with severe hypertensive disease in whom it is important to lower the pressure without delay, we know of no more effective treatment than the combination of a ganglion-blocking drug with an oral diuretic of the chlorothiazide group.

Since ganglion-blocking drugs have not yet been superseded a review of their present uses is not inappropriate.

GENERAL PRINCIPLES

It must be remembered that ganglion-blocking drugs are very potent agents for lowering blood pressure and, especially in combination with chlorothiazide or similar preparations, the pressure can be lowered to almost any extent in most patients but not without side-effects. It must therefore be decided not only whether it is desirable to lower the blood pressure at all but, if so, to what extent.

In general, a raised blood pressure is not in itself an indication for administering potent drugs, especially in middle-aged women. With the exception of relatively young men with a high diastolic pressure, we consider that they should only be given if there is also evidence of secondary

changes in the fundi or heart. This is because there is not, as yet, an entirely satisfactory drug or one without unpleasant side-effects and, logically, once begun, treatment should be continued for life in most cases. This is a heavy sentence.

In particular, there are many patients in whom the blood pressure should only be reduced to a moderate degree and in whom severe postural falls must at all costs be avoided. Such cases include those with evidence of coronary or cerebral atherosclerosis and those with impairment of renal function of sufficient severity to be reflected in a raised blood urea. In patients with coronary-artery disease angina pectoris may be induced or aggravated. Myocardial infarction may follow a severe fall in pressure. In those with cerebral atherosclerosis mental changes or cerebral infarction may be induced. In those with impairment of renal function the blood urea may rise or œdema may develop.

Strong indications for lowering the blood pressure to as near normal standing levels as possible, so long as undue side-effects can be avoided, include encephalopathy, retinopathy, left ventricular failure (and even left ventricular hypertrophy alone), cerebrovascular accidents (without evidence of diffuse atherosclerosis) and uncomplicated high diastolic hypertension alone in young men.

THE HYPERTENSION CLINIC

As a rule, the family doctor is not in a position to decide whether treatment is necessary. If errors are to be minimized, this decision requires not only multiple readings of the blood pressure (including basal and sleeping records), and the exclusion of any underlying cause or associated disease such as atheroma, but also ophthalmoscopy, radiography, electrocardiography, and assessment of renal function. Furthermore, it is usually much better that treatment should be started, and if possible stabilized, in hospital. Some may think this a counsel of perfection, and there are obvious difficulties and disadvantages in referring all patients with hypertension to hospital. Our experience, however, shows that many patients are at present receiving treatment which is inadequate or unnecessary; and if one accepts the fact that hypertension is a potentially serious condition, that treatment is difficult, and that once initiated it should logically be continued for life, then it seems only right that, wherever the patient may live, the best possible arrangements should be made. The more cases one sees, the more one appreciates the difficulties of proper selection and of the avoidance of error.

In older patients special investigations such as pyelography are rarely indicated, and often only moderate reduction of the blood pressure is desirable. In general, the younger the patient the more important is it to exclude underlying disease and to treat the hypertension thoroughly.

We have no doubt that the best means of ensuring satisfactory control of a patient with serious hypertensive disease is his attendance at a clinic or-

ganized for the purpose. Likewise, the blood-pressure records are most likely to be accurate if they are always taken by the same technician—and usually the readings will be lower than a doctor's because the technician is a lesser stimulus for an emotional rise of pressure. In the early days after discharge from hospital a stable regime can be most speedily and safely ensured in a clinic. Although the intervals between visits can gradually be increased, regular attendance gives the patient an opportunity to discuss difficulties and the doctor an opportunity for serial recordings of objective changes in retina, heart, and renal function.

The practitioner has an important part to play in detecting the need for referral in the first place, in supervising treatment and dealing with side-effects, in explanation, encouragement and reassurance, in doing what is possible to minimize stress and ensure that work is suitable and also in advising on many a relevant domestic matter. With these principles in mind we can now consider the various ganglion-blocking drugs which are available and in use in this country.

GANGLION-BLOCKING DRUGS

All compounds in this group act by blocking the transmission of nerve impulses through the synapses of autonomic ganglia. They have no central action and their effect is largely dependent upon posture. The blood pressure is little reduced in the lying position and a little more in the sitting position and their full effect is only achieved when the patient is standing. Our observations have shown that raising the head of the bed on blocks has no appreciable effect.

Methonium compounds.—Our experience with the early methonium compounds, especially pentamethonium and hexamethonium was reviewed in *The Practitioner* nine years ago (Turner, 1951). Poor and irregular absorption from the gastro-intestinal tract made oral administration unreliable and also dangerous, largely on account of syncope and paralytic ileus, so that parenteral treatment was necessary. There were obvious disadvantages in self-administration by injection three times a day and since these compounds are no longer recommended they will not be discussed further. Except in emergency we have not given any drug for the treatment of hypertension by injection since 1954.

Pentolinium.—The introduction of pentolinium was a definite advance because of improved absorption and longer duration of action. In our experience, this is still a useful drug and substances subsequently introduced have seemed to hold little advantage but, since pentolinium has fallen out of fashion and because it is best for the practitioner and hospital staff to have to deal with as few compounds as possible, we do not start new patients on it. Further, there are theoretical advantages in the newer drugs which may become obvious in a larger series. Some of our patients, however, continue to have their blood pressure satisfactorily controlled after five years.

Mecamylamine, which was introduced in 1956, is a secondary amine, in contrast to the methonium compounds and pentolinium which are tertiary, amines. It is better absorbed and its action is of longer duration than the latter substances and it was hoped that these attributes would lead to smoother control of the blood pressure than with pentolinium. In our experience, however, side-effects have been just as frequent and severe and

Drug	Availability	Dosage (thrice daily)	Average daily maintenance dose
Pentolinium	Tablets of 40 and 200 mg.	40 mg. initially, each dose gradually increasing by increments of 40 mg.	600 mg.
Mecamylamine	Tablets of 5 and 10 mg.	2.5 mg. initially, each dose gradually increasing by increments of 2.5 mg.	60 mg.
Pempidine	Tablets of 5 and 10 mg.	2.5 mg. initially, each dose gradually increasing by increments of 2.5 mg.	25 mg.
Chlorisondamine	Tablets of 50 mg.	25 mg. initially, each dose gradually increasing by increments of 25 mg.	400 mg.
Pentacynium	Tablets of 100 mg.	50 mg. initially, each dose gradually increasing by increments of 50 mg.	800 mg.

TABLE I.—Recommended regime of dosage of various ganglion-blocking drugs.

tolerance develops in some patients. This drug has the disadvantage of slow excretion so that unwanted side-effects are liable to persist for several days. We concluded that any theoretical advantages claimed for mecamylamine on the basis of its pharmacological properties were not reflected in practice and its advantages over pentolinium were slight (Kitchin, Lowther and Turner, 1957). Nevertheless it is a useful drug and reasonable control over the blood pressure can be maintained in most cases.

Pempidine was introduced in 1958. It is structurally related to mecamylamine and is as easily absorbed but differs in certain respects which, it was thought, might make it a better drug for the treatment of hypertension. In particular, it was considered that its property of more rapid and complete excretion might be helpful in enabling initial dosage to be worked up more quickly and side-effects should be more short-lived. These potential advantages, however, were hardly appreciable in practice and, although it is a potent drug for lowering the blood pressure, the same familiar difficulties in administration were found as with other ganglion-blocking drugs (Kitchin, Lowther and Turner, 1960). Nevertheless, because pempidine has no relative disadvantages and at least the theoretical advantage of more rapid

excretion, we do at present consider it to be the ganglion-blocking drug of choice.

Chlorisondamine and pentacynium are two other ganglion-blocking drugs which we have used and found effective in lowering the blood pressure but, since they produce the usual side-effects and offer no special advantages, they have not achieved popularity.

RECOMMENDED REGIME

It is best to start with a small dose of a single preparation given three times daily and gradually work up by increasing each dose on alternate days (table I) until a significant fall in standing diastolic blood pressure is obtained. Thereafter increments must be made cautiously in order to avoid severe postural hypertension because dosage may be critical. Some degree of tolerance is common but this tends to disappear within a few weeks or months. Side-effects are usual but the patient can be encouraged that with patience, perseverance and appropriate treatment these will become 'ess troublesome. Individual sensitivity varies considerably and there is a wide range in the dose which is effective in controlling the blood pressure and in producing side-effects.

If there is difficulty in controlling the pressure without undue side-effects the first step should be to lower the dose and add hydrochlorothiazide as described below; if this is not sufficient, the appropriate antidote for each side-effect must be given.

Recommended regime for severe hypertension.—For a patient in hospital with severe diastolic hypertension together with retinopathy, left ventricular failure or peripheral œdema in whom it is desirable to lower the blood pressure as soon as possible we advise beginning with hydrochlorothiazide, 25 mg. three times daily for three days. Pempidine, 5 mg. three times daily should then be added and the dose increased by 2.5 mg. every other day until the pressure is controlled. Rarely, for example if it is felt desirable to lower the blood pressure rapidly on account of encephalopathy, a soluble preparation can be given intravenously and repeated as required in order to lower the blood pressure to a moderate degree and thereafter treatment can be continued by mouth. Caution is required because encephalopathy is sometimes mistaken for a cerebrovascular accident.

COMBINATION WITH CHLOROTHIAZIDE

Chlorothiazide and related compounds do not by themselves lower the blood pressure. On the other hand, they have a potent adjuvant action when used in combination with ganglion-blocking drugs and this fact is of great value in the treatment of hypertension, especially in relatively resistant cases when it is important to lower the blood pressure quickly or when side-effects from parasympathetic blockade are troublesome. It may well be that a small dose should always be combined with each dose of the ganglion-blocking drug but we have not adopted this as a routine.

The maximum dose that need be prescribed in most cases is 25 mg. of hydrochlorothiazide three times daily; if this amount is not exceeded electrolytic disturbances from loss of potassium are unlikely to occur and no potassium supplement is necessary. It should be remembered that hypokalæmia will contribute to the development of ileus. In our opinion hydrochlorothiazide should certainly be given from the outset in patients with hypertensive retinopathy, left ventricular failure or peripheral œdema. It is very important to reduce the dose of the ganglion-blocking drug at the same time as chlorothiazide is added, or dangerous hypotension may occur. The dosage may be halved in the first instance and then gradually and cautiously increased.

COMBINATION WITH RAUWOLFIA

It has often been recommended that the combination of Rauwolfia with the ganglion-blocking drug not only enables smoother control of the blood pressure to be obtained in the first instance with fewer side-effects, but also a smaller dose of the ganglion-blocking drug is necessary. In our experience, however, about 50 per cent. of all patients are insensitive to these drugs and in a considerable proportion of the remainder their effect is too slight to be of any value. Moreover if, after a few months of treatment with the combination, the Rauwolfia drug is stopped it will be found that the blood pressure does not rise appreciably in more than about 10 per cent. of patients. In these circumstances we rarely advise their use.

Reserpine itself should never be prescribed because of its dangerous propensity to induce serious depression. Many patients have lost their lives by suicide and many others have had to be admitted to mental hospitals for treatment. Related compounds which have been more recently introduced may have fewer side-effects but in our opinion this group of drugs is of very limited value.

PRACTICAL DIFFICULTIES IN THE ADMINISTRATION OF GANGLION-BLOCKING DRUGS

Excessive postural hypotension can hardly be classed as a side-effect, being the direct action of the drug, but its occurrence is not always easily prevented if the blood pressure is to be well controlled. It can be a troublesome and even dangerous feature of therapy. This effect differs only in degree from the object of treatment, i.e. a postural fall in pressure. In some measure this property may be utilized to diminish the number of blood-pressure recordings which need be made because the dose can be increased until mild symptoms appear on standing still, and then slightly reduced. The first symptom of undue hypotension is that of dizziness while standing still—as when shaving or waiting for a bus. Factors such as fever, a hot bath, hot weather, a purgative, or taking the drug on an empty stomach or with a diuretic may sometimes engender postural hypotension and the patient

should be informed about these points. If dizziness is troublesome the dose must be reduced and if it occurs regularly at one particular time of day the dose immediately preceding this time should be reduced. Because dosage is often critical this trouble may recur with each increment. If the effects are slight, however, dizziness from postural hypotension tends to pass off with dose reduction owing to the development of minor degrees of tolerance.

SIDE-EFFECTS

The side-effects of ganglion-blocking drugs are numerous and, although falling into the same general pattern, vary somewhat from patient to patient, reflecting differences in autonomic make-up. They are mainly the result of parasympathetic blockade. In all cases the first step should be to decrease the dose of the ganglion-blocking drug and add hydrochlorothiazide or a related compound. In order to avoid undue hypotension it is best in the first instance to halve the dose of the ganglion-blocking drug and then add a small quantity of the diuretic to each dose as described below and then gradually to work up the dose of the ganglion-blocking drug until the blood pressure is again controlled. Should this not be sufficient to minimize side-effects, other measures are available. In general, the next step should be to give a drug which stimulates parasympathetic nerve-endings. Neostigmine is useful for this purpose and is best given at the same time as the ganglion-blocking drug, beginning with half a tablet (7.5 mg.) three times daily and gradually working up. Often a larger dose will be found advisable in the morning to assist bowel action.

Blurring of vision is due to paralysis of accommodation and tends to be most troublesome in the early days of treatment. Improvement may be obtained with eserine (0.5 to 1 per cent.) or pilocarpine (1 per cent.) drops or a combination of the two. If this is not sufficient, slip-on lenses may be tried and if these are ineffective and the difficulty persists, permanent spectacles can be given.

Dryness of the mouth rarely persists to a troublesome degree and sucking sweets, such as acid drops, may help. If necessary, pilocarpine pills, $\frac{1}{12}$ grain (5 mg.), can be taken before meals as required. The complaint may be of a bad taste in the mouth. Glossitis occasionally develops and may respond to cyanocobalamin.

Constipation is a common and important side-effect which must be controlled or paralytic ileus may follow. No more than twenty-four hours should be allowed to pass without taking remedial action. A regular aperient is usually required and a satisfactory regime must be found for each patient. When distension is associated with constipation oral neostigmine should be tried in a dose of 7.5 to 15 mg. twice daily.

Paralytic ileus is a dangerous complication and every precaution should be taken to avoid it. It is best for the patient to be admitted to hospital. If symptoms are severe the drug must be stopped, neostigmine injected three

to four times daily, and enemas given as required; an intravenous drip and gastric suction may be necessary. Intelligent anticipation should prevent the numerous deaths which were reported in early days.

Diarrhœa usually, but not always, follows constipation and occurs most often with mecamylamine. It may be troublesome and difficult to overcome. The dosage of the ganglion-blocking drug should be reduced, after which it can be gradually increased again and a chalk mixture given.

Retention of urine may occur, especially in middle-aged males. Sometimes there is delay in emptying the bladder but this tends to pass off. Neostigmine is of value and should first be tried by mouth. Carbachol is also useful.

Impotence may be troublesome but an unavoidable price to pay for adequate control of the blood pressure.

General malaise is experienced by most patients on ganglion-blocking drugs but may only be realized if for any reason treatment has to be stopped. This effect is one good reason why treatment for hypertension should not be given unless really necessary.

Œdema and the general picture of cardiac failure sometimes develop owing to the retention of salt and water consequent upon a reduction in glomerular filtration rate due to a fall in cardiac output. In such cases it is usually necessary to be satisfied with less strict control over the blood pressure, but the combination of reduction in dosage and the addition of an oral diuretic of the chlorothiazide type may suffice.

Central nervous system disturbances.—Mecamylamine and pempidine can pass the blood-brain barrier and various disturbances of the central nervous system have been reported. Coarse or flapping tremor, which disappears during sleep, and a variety of mental changes including agitation, depression and hallucinations may occur when high dosage is used in patients with impaired renal function.

TOLERANCE, SENSITIVITY, AND RESISTANCE

Tolerance.—Tolerance occurs in varying degree with all ganglion-blocking drugs but tends to be less severe with pempidine and mecamylamine than with hexamethonium or pentolinium. Tolerance signifies that after the desired hypotensive response has been produced a steady increase of the dose is necessary in order to maintain the response. The disadvantages of this are that the patient must return to the clinic at short intervals, only to be discouraged by the change in treatment, that side-effects become more frequent and severe and in the end control over the blood pressure may be lost. Occasionally tolerance develops rapidly and the consequent rise in pressure between visits to the clinic may have serious results. As tolerance develops the dose of the drug should be increased slowly because even a small increase may result in control being regained. Unfortunately, side-effects which have decreased may return with each rise in dose. Some degree of cross-tolerance may occur between one ganglion-blocking drug and another.

Sensitivity.—Whilst there is no doubt that the dose contained in the smallest single tablet supplied by the manufacturers of each of the ganglion-blocking drugs will usually prove to be a suitable starting point for the treatment of most patients some individuals are exceptionally sensitive. For this reason it is best to begin with half a tablet three times daily. Relatives and hospital staff should be aware of the possible occurrence of hypotensive phases in the early stages of treatment and the appropriate advice be given as to how to deal with it. The effects can usually be reversed by lying the patient down and lifting the legs or end of the bed.

Resistance.—Resistance implies that as successive increments in dosage are made the blood pressure remains unchanged even at very high levels. When this occurs the patient does not usually experience side-effects but failure to control the blood pressure over weeks of increasing doses may, itself, be a source of danger. The addition of a chlorothiazide drug or placing the patient on a low-salt diet in addition to the ganglion-blocking drug may produce the desired effect. To ensure that faulty absorption is not to blame, the drug may be tried by injection; if the blood pressure is resistant to this another drug should be tried.

SUMMARY AND CONCLUSIONS

Ganglion-blocking drugs have not yet been superseded for the treatment of severe hypertension and those in common use are reviewed.

It is concluded that there is little to choose between them but pempidine is probably the best available at present.

If the blood pressure is difficult to control or if side-effects are troublesome, combination with an oral diuretic of the chlorothiazide type should be tried.

The treatment of side-effects is discussed.

The selection of patients for treatment and general principles of management are also briefly considered.

The search for a satisfactory hypotensive agent should continue.

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SYMPATHETIC-BLOCKING DRUGS IN THE MANAGEMENT OF HYPERTENSION

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With hypotensive treatment now an established branch of therapeutics it is difficult to realize that less than twenty years ago it was considered doubtful if a hypertensive patient would tolerate reduction of blood pressure. It was the success of lumbo-dorsal sympathectomy which finally allayed these fears and laid the foundation for modern drug treatment of hypertension.

The development and continued improvement of ganglion-blocking drugs represents a considerable achievement but within the last year or two there have been signs that the capabilities of this type of drug had been fully exploited: despite every improvement their ultimate effectiveness as hypotensive agents has continued to be restricted by the undesired effects of parasympathetic blockade which appear inescapable—at least with high dosage. Lacking precise knowledge of the causes of hypertension, release of peripheral vasomotor tone still seemed to offer the most effective means of controlling blood pressure but there was an obvious need for a drug which would achieve this by blockade of sympathetic nerves alone. Eagerly though this was awaited it could scarcely have been anticipated that on a single day we would be offered the choice of two drugs with such action; yet, by a singular coincidence the first reported trial of bretylium tosylate in this country (Boura *et al.*, 1959) and that of guanethidine in the United States (Page and Dustan, 1959) were published simultaneously.

Although chemically these drugs appear entirely unrelated, their principal actions are remarkably similar and have shown beyond doubt that the hypotensive effect in both cases is due to peripheral inhibition of sympathetic nerve action (table I). Neither the nature nor the exact site of the blockade is yet known although the reduced catechol-amine content of certain organs following guanethidine suggests in this case a possible affinity with reserpine. It will be noted also that the difference in absorption and excretion of the two drugs will account to a large extent for the contrast in their clinical actions.

BRETYLIUM TOSYLATE AS A HYPOTENSIVE AGENT

The first trial of bretylium tosylate in hypertensive patients gave encouraging results. When a single dose was taken by mouth it was found that postural hypotension developed within 1½ to 3 hours, persisting in some cases as long as nine hours, and after seven months' experience in the use of the drug

during which 36 patients received regular treatment Boura and his colleagues (1959) were able to report that in nearly every case the blood pressure had been effectively controlled without symptoms of parasympathetic blockade. The dosage employed varied from 200 to 3,900 mg. daily and, although sudden episodes of severe postural hypotension were encountered, it was

	Bretylium tosylate	Guanethidine
Formula	N-O-bromobenzyl-N-ethyl : N : N-dimethyl ammonium p-toluene sulphonate.	2-perhydroazocin-1^3-ylethyl-guanidinium sulphate.
Hypotensive action	In anæsthetized cats intravenous injection of 0.5 to 5 mg./kg. lowered blood pressure. With smaller doses the hypotensive effect was mainly postural.	In unanæsthetized normotensive dogs intravenous injection of 7.5 to 15 mg./kg. caused only a slight reduction of diastolic pressure but in dogs with experimentally induced hypertension blood pressure was markedly reduced. Oral administration to hypertensive dogs caused a pronounced and sustained fall of blood pressure.
Effects on nictitating membrane	In cats, subcutaneous doses of 5 to 10 mg./kg. and oral doses of 30 mg/kg. caused relaxation of the nictitating membrane which developed fully in 18 to 36 hours. While under the influence of the drug stimulation of the cervical sympathetic nerves whether proximal or distal to the ganglion failed to cause contraction but at the same time the nictitating membrane was found to be hypersensitive to adrenaline and noradrenaline injected intravenously.	In dogs and cats, intravenous injection of 10 to 15 mg./kg. caused relaxation of the nictitating membrane within 6 to 12 hours; this effect persisting for 1 to 2 weeks. While under the influence of the drug the nictitating membrane could not be contracted by pre-ganglionic stimulation of the cervical sympathetic, although (except for a limited period) conduction across the ganglion and in pre-ganglionic fibres appeared to be normal. At the same time the nictitating membrane was shown to be hypersensitive to injected adrenaline and noradrenaline.
Pressor responses:		
Splanchnic nerve stimulation	Unaffected	Unaffected
Carotid artery occlusion	—	Abolished
Amphetamine	Reduced	Reduced or abolished
Ephedrine	—	Reduced or abolished
Tyramine	—	Reduced or abolished
Noradrenaline	Enhanced	Usually enhanced
Adrenaline	Enhanced	Usually enhanced
Vasopressin	—	Usually enhanced
Hypertensin	—	Usually enhanced
Catechol-amine content of tissues	Unchanged in adrenal medulla (cats and rats) and in sympathetic ganglia (cats).	Unchanged in adrenal medulla and brain but reduced 75 to 85 per cent. in heart and 60 per cent. in spleen within 4 to 18 hours after a single dose: normal content regained in 7 days (rabbits and cats).
Distribution of drug	Predominantly in sympathetic ganglia and adrenergic nerves.	Predominantly in kidneys.
Absorption and excretion of drug	5.1 to 18.3 per cent. (mean 13.9 per cent.) of oral dose excreted in urine in 24 hours (maximal excretion rate 2 to 8 hours). Negligible excretion after 24 hours.	16.8 to 29.3 per cent. (mean 23.7 per cent.) of oral dose excreted in urine in 24 hours (maximal excretion rate 2 to 4 hours). 27.5 to 41.1 per cent. (mean 35.9 per cent.) of oral dose excreted in urine in 72 hours.
Inference	'Bretylium tosylate selectively blocks the peripheral sympathetic nervous system by action on the adrenergic nerves in which it selectively accumulates' (Boura *et al.*, 1959; Dollery *et al.*, 1960a).	'Guanethidine inhibits the release and/or distribution of transmitter substances from sympathetic nerve terminals' (Cass *et al.*, 1960; Dollery, Emslie-Smith and Milne, 1960; Maxwell, Mull, and Plummer, 1959; Page and Dustan, 1959).

TABLE I.—Principal features and actions of bretylium tosylate and guanethidine.

found that fairly smooth control could be achieved if the drug was taken at eight-hour intervals. It appeared best to start with a dose of 200 mg. three times daily and to increase this subsequently by 100 mg. daily. Some patients appeared to develop slight tolerance but at this stage this did not cause any difficulty. Stuffy nose was the only side-effect identified.

Unhappily, with the drug gaining a wider circle of acquaintance, reports began to appear which were distinctly less favourable (Smirk and Hodge, 1959; Dollery *et al.*, 1960a; Turner and Lowther, 1960a, b; Evanson and Sears, 1960). Lists of side-effects grew longer and these included parotid pain, muscle weakness, diarrhœa and visual blurring, but more serious than these were complaints about the instability of the blood pressure, resulting in sudden and unpredictable hypotensive attacks, and the increasing difficulty of maintaining blood pressure control due to tolerance. As has been observed with guanethidine (Leishman *et al.*, 1959) and on occasions even with ganglion-blocking drugs (Rønnov-Jessen, 1953) exercise not uncommonly was responsible for calamitous attacks of hypotension. In other cases, however, severe hypotension developed unexpectedly without this provocation and it has been suggested (Dollery *et al.*, 1960a) that drug-retention due to renal impairment might account for these episodes. Estimates of the proportion of cases with successfully controlled blood pressure varied in these reports from 50 to 75 per cent., but even at an early stage it was evident that most of the patients were developing tolerance and that, although their blood pressure continued to be controlled, this was only at the expense of steadily increasing dosage.

As treatment with bretylium continued these difficulties increased and after conducting a trial for eighteen months Dollery and his colleagues (1960b) finally reported that they had been forced to abandon the drug since almost all their patients were now resistant including those who earlier had done well. (Recently, Lowther and Turner (1960) have described a trial of bretylium which ended similarly.) Although by the elimination of parasympathetic blockade the development of bretylium marked a 'breakthrough' in hypotensive therapy, it must be accepted in face of this evidence that in its present form the drug is unsuitable for long-term treatment of hypertensive patients. Lack of consistency in hypotensive action and tolerance which develops during treatment have proved to be the main failings of bretylium. The behaviour of guanethidine in these two respects is likely therefore to be examined with special care.

GUANETHIDINE AS A HYPOTENSIVE AGENT

Meanwhile in the United States guanethidine had also made a promising debut and it was established by the earliest clinical trials (Page and Dustan, 1959; Richardson and Wyso, 1959; Frohlich and Freis, 1959) that, when taken by mouth, this drug similarly reduced blood pressure without parasympathetic blockade. As with bretylium and ganglion-blocking drugs the

hypotensive effect was predominantly but not exclusively postural, but the distinctive feature of guanethidine's action was the delayed onset and prolonged duration of the hypotensive effect. Although the dosage employed during these trials varied from as little as 12.5 mg. up to 400 mg. daily this was seldom less than 75 mg. and postural syncope and confusion were often encountered during treatment. No toxic effects were reported but diarrhœa appeared to be a common side-effect.

Being largely preoccupied at this stage with the evaluation of bretylium it is perhaps not surprising that, initially, guanethidine did not attract wide attention in this country. At the Royal Infirmary, Sheffield, however, a trial

Stage of trial	Duration of treatment (weeks)	Total cases treated	Adequate blood-pressure control		Range of dosage (mg.)	Daily dose in controlled cases					
						<20 mg.		20 to 60 mg.		>60 mg.	
			No. of cases	%		No. of cases	%	No. of cases	%	No. of cases	%
I	3-11	25	18	72	10-60	1	5.5	17	94.5	0	0
II	4-24	43	33	76.7	10-95	3	9.1	24	72.7	6	18.2
III	8-54	100	81	81	10-150	4	4.9	61	75.3	16	19.8

TABLE II.—Blood-pressure control and dosage of guanethidine at three stages of clinical trial

of guanethidine was started at this time and after experience of treating 100 patients (five patients who died—three from strokes, two from congestive heart failure—are not included in this total) for periods ranging from two to fourteen months it is possible to make a fair appraisal of the drug's capabilities. Although, surprisingly, only one of these patients had papillœdema, the majority had severe hypertension and in 80 per cent. the diastolic pressure before treatment was not less than 130 mm. Hg. A number of them had previously been treated with ganglion-blocking drugs and in most of these the transfer to guanethidine was made without admission to hospital.

DOSAGE OF GUANETHIDINE

Early results confirmed that guanethidine was an effective hypotensive drug (Leishman, Matthews and Smith, 1959), but it soon became evident that, although individual sensitivity varied considerably, the range of dosage employed in the American trials was far too high for the average case. Alarming hypotensive reactions and side-effects were encountered, especially in the 2nd and 3rd weeks of treatment, before it was appreciated that treatment must start with small doses and, of equal importance, that subsequently these should not be increased too rapidly. After some patients had been found to be exceptionally sensitive to guanethidine (four patients, for example, remain well controlled on a daily dose of 10 mg.), starting dosage

was eventually restricted to 10 or 20 mg. daily, the choice being decided according to the blood-pressure response after a single test dose of 30 mg. Until satisfactory blood-pressure readings were obtained dosage was reviewed weekly, and if necessary was increased by not more than 10 mg. daily. In some cases even a change of 5 mg. had a marked effect. Apart from permitting larger increments in the case of relatively resistant patients who

Complication	Incidence (per cent.)	
Orthostatic hypotension	Severe	7
	Moderate or slight	46
Diarrhœa	Severe	10
	Moderate or slight	37
Muscle aching and weakness	Severe	3
	Moderate or slight	41
Water retention	Severe	11
	Slight (weight gain exceeding 2 kg.)	33
Exertional dyspnœa	Severe	2
	Moderate or slight	38
Parotid pain		2
Nasal stuffiness		3

TABLE III.—Incidence of complications among 100 patients treated with guanethidine.

were already taking high doses, this scheme of treatment has been adhered to throughout the trial and since its adoption neither hypotensive complications nor side-effects have presented any real problem. Above all, treatment with guanethidine demands patience, and any attempt to accelerate its tempo (Dollery, Emslie-Smith and Milne, 1960) appears to be scarcely justified unless the patient can be kept under close and continuous observation.

So far, a daily dose of 150 mg. has not been exceeded and at present 75 per cent. of the patients require less than 60 mg. daily. The day's requirement of the drug was usually given in a single dose taken after breakfast. Division of the dose only appeared helpful in a few patients who complained particularly of hypotensive symptoms during the morning.

Effect on blood pressure.—It was found that the fall of blood pressure following guanethidine was gradual and progressive, commonly reaching its lowest level some seven days after an increase of dose and remaining stabilized at this level until dosage was again altered. On two occasions when treatment was stopped blood pressure did not return to its original level in less than four days. A slight drop of blood pressure was often observed four hours after the drug was taken and from studies of renal excretion (table I) it seems now certain that this is due to the drug being absorbed maximally at this time. Apart from this effect at four hours the diastolic pressure showed little diurnal fluctuation during treatment with guanethidine. This feature

greatly simplified its management since dose adjustment could be based on the blood pressure recorded at any time of day regardless of when the drug was last taken.

Tolerance and blood-pressure control.—Despite its obvious potentialities as a hypotensive agent, no advantage could be claimed for guanethidine without an assurance that continuous treatment with this drug will not be handicapped like bretylium by the development of tolerance. Tolerance in fact does occur when patients are treated with guanethidine and during the Sheffield trial 23 per cent. of cases, after being stabilized, required later an increased dose, but in only one case has tolerance led to complete loss of blood-pressure control. Whether tolerance has presented an appreciable problem, however, may perhaps best be gauged by comparing the proportion of patients with satisfactorily controlled blood pressure at three succeeding stages of the trial together with the range of dosage employed at these times. (The term 'satisfactorily controlled blood pressure' would be difficult to define but in this analysis no patient so described showed a reduction of standing diastolic pressure which was less than 20 mm.Hg, and in the majority the fall was greater.

From the figures shown in table II, which summarizes the state of the trial after three, six and twelve months, respectively, it is reassuring to see that although blood-pressure control has improved steadily throughout the trial there is no indication that this has been achieved at the expense of consistently increasing dosage. Four patients out of the 100 treated have so far remained resistant to guanethidine.

COMPLICATIONS OF GUANETHIDINE

No toxic effects from guanethidine have been noted but, as with other hypotensive drugs, at the outset of treatment there was often some increase of blood urea but in most cases this was transient. On the other hand it will be seen (table III) that the incidence of hypotensive symptoms and side-effects in the Sheffield series of cases was not inconsiderable although these figures undoubtedly exaggerate their importance. Reactions of any severity were almost invariably due to overdosage, and these were seldom seen in the later stages of the trial when experience had been acquired in using the drug.

Most of these complications were encountered also during treatment with bretylium although their relative importance differs in the case of the two drugs. With guanethidine, for example, parotid pain has not presented any problem and patients seldom developed serious hypotensive symptoms as a consequence of exercise. Diarrhœa, on the other hand, was often troublesome and complaints of muscle aching and weakness also appear to have been more common than with bretylium. Early in the trial, when dosage was excessive, these muscle symptoms were in fact distinctly alarming but more usually they presented in a mild form and were always relieved when the

dose was reduced. Muscle tremor (Dollery, Emslie-Smith and Milne, 1960) was not observed in any of these cases. Patients treated with guanethidine usually had bradycardia and it is, of course, probable that most of the male patients developed failure of ejaculation during treatment.

Unquestionably the most puzzling complication of guanethidine is its tendency to cause water retention. In many cases this was symptomless and was only recognized by rapid gain in weight. Occasionally, however, the syndrome presented in more severe form as a clinical state indistinguishable from congestive heart failure, with increased jugular venous pressure, severe dyspnœa, œdema and, rarely, ascites. Although no disturbance of serum levels, or excretion, of electrolytes has consistently been present in these cases and its explanation has still to be found, this situation was normally restored without difficulty by diuretics such as hydrochlorothiazide although in some cases these had to be continued for long periods. It was observed that blood-pressure control was often temporarily lost during the phase of water retention but was regained following its elimination.

DISCUSSION

After a late start guanethidine has finally caught up with bretylium and by now both drugs may be regarded as adequately tested. Unfortunately, future interest in bretylium is likely to be mainly historical as, due both to tolerance and the unpredictability of its hypotensive action, it has proved unsuitable for the continued treatment of hypertensive patients.

Guanethidine, on the other hand, does not suffer from either of these disadvantages for in the course of twelve months' treatment only a minor degree of tolerance was encountered and it was usually found that the blood pressure responded as anticipated to each alteration of dose. With guanethidine, however, orthostatic hypotension and side-effects have been the main source of trouble. It is not altogether surprising that patients taking guanethidine have been more conscious of hypotensive symptoms than when treated with ganglion-blocking drugs since, because of the restricting influence of parasympathetic effects, the latter were seldom given in comparable dosage. With guanethidine also the hypotensive effect is of much greater duration. Although hypotensive symptoms are thus essentially an expression of guanethidine's potency their prevalence has emphasized the limitations of this method of treating hypertension. On a number of occasions transient but repetitive neurological manifestations accompanying hypotension have drawn attention to cerebral vascular insufficiency which was previously unsuspected and in the light of this experience it is clear that the treatment of older subjects with guanethidine must be conducted with some vigilance. Symptoms suggestive of carotico-vertebral stenosis should undoubtedly be regarded as an absolute contraindication to its use.

The majority of the side-effects of guanethidine are caused by overdosage

and thus to a large extent may be avoided; indeed in a recent experience less than one-third of the patients treated were reported to have had symptoms which were more than trivial (Dollery, Emslie-Smith and Milne, 1960). Two complications, however, are less closely related to size of dose. Severe diarrhœa (for which codeine in ½-grain (30 mg.) doses usually proved a reliable remedy) has, for example, occasionally developed without accompanying hypotension and in the water-retention syndrome overdosage also appears to play no part.

There is no doubt that patients treated with guanethidine need individual attention and those who employ the drug should not only be aware of the early symptoms of overdosage but be prepared also to pay attention to their patients' complaints. When circumstances otherwise do not require their admission to hospital, treatment can be conducted without difficulty on an outpatient basis although preferably this will be in a clinic organized for this purpose where experience in the use of the drug can more rapidly be acquired. At the beginning of treatment when dosage is often changing, it is wise for patients to be seen at intervals of one to two weeks, but once the standing diastolic pressure has been stabilized at an appropriate new level it has seldom seemed necessary for them to attend more often than once in six to eight weeks. In addition to recording the blood pressure (in lying and standing positions) and making periodic checks of renal function at these visits, it has been found valuable to maintain throughout treatment an accurate record of each patient's weight. On a number of occasions the development of water retention has been recognized at an early stage by a patient's unexpectedly rapid gain of weight.

Reduction of vasomotor control is admittedly a somewhat crude method of treating hypertension and, however effective it may be, the patient's comfort will always present a limiting factor. Targets for hypotensive therapy are often set too high. In a severely hypertensive patient, for example, any attempt to reduce the standing blood pressure to a normal level is almost bound to cause distress and is probably unnecessary. It will be recalled that relatively modest falls of blood pressure following sympathectomy had a remarkably favourable effect on prognosis (Leishman, 1959).

Provided it is used carefully and without impatience the treatment of hypertensive patients with guanethidine presents little difficulty but, as in the case of cerebral vascular disease, some caution obviously is needed when treating patients with angina pectoris or renal failure, and the special propensity of guanethidine to cause water-retention will have to be borne in mind if the drug is to be given to a patient already in heart failure. Hypertension which is mild and benign can usually be controlled effectively by drugs of lesser potency and the obvious role for guanethidine is in the treatment of severe cases. Since guanethidine at the same time assures freedom from constipation and other parasympathetic effects, for this type of case it appears at present to be the drug of choice.

SUMMARY

Despite every modification and improvement the hypotensive action of ganglion-blocking drugs remains hampered by parasympathetic effects.

Bretylium tosylate and guanethidine reduce blood pressure without parasympathetic blockade by selective inhibition of sympathetic nerve action.

The hypotensive effect of both drugs is predominantly postural and in the case of guanethidine is prolonged.

Bretylium has proved disappointing, since its hypotensive action is commonly unpredictable and tolerance develops increasingly as treatment continues.

Guanethidine is free from these faults but treatment may be complicated by orthostatic hypotension and side-effects unless dosage is adjusted carefully to each patient's requirement. Its management, however, is not difficult provided dosage initially is small and subsequently is increased slowly.

Blood pressure is now adequately controlled in 80 out of 100 patients who have been treated with guanethidine for two to fourteen months. On the basis of this experience it is suggested that for severely hypertensive patients guanethidine is at present the drug of choice.

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HYPOTENSIVE DIURETICS

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CHLOROTHIAZIDE and its derivatives play an important and often primary part in the treatment of selected patients with hypertension. Given alone these diuretics may not induce any striking reduction in blood pressure, but they greatly potentiate the action of other hypotensive drugs, the dosage of which can be reduced with a consequent lessening of unpleasant side-effects. Furthermore, used in combination, chlorothiazide and other hypotensive agents achieve a smoother control of the blood pressure without sudden fluctuations. In some particularly severe refractory cases satisfactory control may only be achieved by adding the synergistic action of chlorothiazide to more potent agents.

MODE OF ACTION

Experimental evidence suggests that the fall in blood pressure produced by chlorothiazide is due to a reduction in the patient's plasma and extracellular fluid volumes. After an initial diuresis of water and sodium lasting about three days, a new equilibrium is established with the extracellular fluid volume 1 to 2 litres less than the pre-treatment value and the plasma volume reduced by 10 to 15 per cent. (Tapia *et al.*, 1957; Freis, 1959; Dollery *et al.*, 1959). Infusion of salt-free dextran will restore the blood pressure to its former value, indicating that the hypotensive effect is related to the reduction in plasma volume rather than to sodium depletion *per se* (Freis, 1959; Dollery *et al.*, 1959). In addition, by making the urine alkaline chlorothiazide tends to retard the renal excretion of mecamylamine and pempidine and so enhances their potency, although the same synergistic action is seen with other antihypertensive agents, the elimination of which is not influenced (Harington and Kincaid-Smith, 1958).

There is little support for the belief that chlorothiazide has a specific hypotensive effect distinct from its diuretic action (Wilkins, 1957). Single intravenous doses have no appreciable effect on blood pressure or on the hypotensive response to a standard intravenous dose of pentolinium (Dollery *et al.*, 1959). Nor is a hypotensive action peculiar to chlorothiazide and its derivatives. Mercurial diuretics, administered parenterally in doses sufficient to cause electrolyte and water loss equivalent to that after chlorothiazide, induce a comparable reduction in blood pressure (Wilkins *et al.*, 1958; McQueen and Morrison, 1960).

INDICATIONS

Whether or not to treat a patient with hypertension is at present indicated more by the physician's philosophy and the custom of the country in which

he practises than by scientific conviction. Although it is difficult to generalize, there is a tendency in Great Britain to treat only those patients with hypertensive *disease*—as shown by symptoms or signs of cardiac, renal or vascular damage—and not patients who have uncomplicated elevation of blood pressure unless this is of extreme degree with a diastolic pressure above 110 to 120 mm. Hg. Patients with lesser degrees of essential hypertension, grade I or II retinopathy, and no evidence of cardiac or renal damage, are best left alone, and attention not directed to their blood pressure for fear of increasing or engendering anxiety. In the United States a rather different attitude obtains, and many patients with uncomplicated hypertension of modest degree receive hypotensive drugs and suffer much mental perturbation with, as yet, no convincing evidence that life is prolonged or complications prevented.

Chlorothiazide alone.—Although in exceptional cases chlorothiazide alone may induce a satisfactory fall in blood pressure, in most instances the effect is not marked (Hollander and Wilkins, 1957; Freis *et al.*, 1958; Moser and Macaulay, 1959; Lee *et al.*, 1960; Smirk *et al.*, 1960). Satisfactory control with chlorothiazide is usually only achieved when the degree of hypertension is small and these are the cases in which there is doubt as to whether any form of treatment is necessary.

Chlorothiazide and reserpine.—The relatively mild hypotensive effect of reserpine may be considerably enhanced by chlorothiazide, the addition of which on average reduces the systolic pressure by a further 25 mm. Hg, and the diastolic level by 10 to 15 mm. Hg. This allows the dosage of reserpine to be kept at a minimum and diminishes the likelihood of undesirable side-effects. This combination is usually only effective in relatively mild degrees of hypertension, in which the indications for treatment are equivocal, but exceptions occur and severe degrees may respond excellently. This form of treatment is particularly useful for patients with hypertension associated with angina pectoris or cerebrovascular disease, in whom a marked fall in blood pressure, or irregularity of control, may induce coronary or cerebrovascular thrombosis.

Chlorothiazide and more potent antihypertensive agents.—The effect of the more potent antihypertensive agents—mecamylamine, hydrallazine, pempidine and guanethidine—is potentiated by chlorothiazide, and if the diuretic is given to a patient already having one of these drugs, the dose of the more potent agent must be reduced by half to prevent a dangerously great fall in blood pressure. The combining of chlorothiazide with a more potent agent has considerable advantages for the patient. First, a smaller dose of the potent agent can be used with a lessening of the liability to undesirable side-effects. Secondly, a more even control of blood pressure is achieved and this may reduce the likelihood of recurrent episodes of postural hypotension on standing. Thirdly, the use of chlorothiazide may control within satisfactory limits the blood pressure of patients who do not respond to other forms of

treatment, singly or in combination, without intolerable side-effects (Lee *et al.*, 1958; Smirk *et al.*, 1960).

The use of more potent anti-hypertensive drugs is always required in patients with malignant hypertension and in most patients with hypertension causing retinal hæmorrhages and exudates without papillœdema (grade III retinopathy). In a proportion of these patients, however, once satisfactory control of the blood pressure has been achieved, it may be possible to maintain the patient on a combination of chlorothiazide and reserpine alone. Except in malignant hypertension, when rapid control of the blood pressure is essential, treatment may be started with chlorothiazide alone or preferably a combination of chlorothiazide and reserpine (0.1 mg. thrice daily). If after a month on this regime the blood pressure is still too high, one of the more potent agents—preferably mecamylamine, pempidine or guanethidine—may be added.

DOSAGE AND CHOICE OF DIURETIC

The diuretic should be given daily; if it is stopped the blood pressure will usually rise in twenty-four to forty-eight hours. An effective dose of chlorothiazide is 500 to 1000 mg. daily, and of hydrochlorothiazide 50 to 100 mg. daily. There is no evidence that any one benzthiadiazine diuretic is more effective than another, or that their effect on potassium excretion is significantly different (McQueen and Morrison, 1960).

TOXIC AND SIDE-EFFECTS

Toxic effects are few in patients being treated for hypertension. Nausea and epigastric discomfort are the most likely to occur and may be less common with hydrochlorothiazide than with chlorothiazide (Smirk *et al.*, 1960; Lee *et al.*, 1960). A temporary increase in blood urea may occur but this is seldom marked unless there is already considerable renal damage, as may be the case in malignant hypertension.

It is perhaps surprising that continued daily treatment does not give rise more often to manifestations of potassium depletion or hypokalæmia. The amount of potassium excreted in the urine depends largely upon the amount of sodium presenting itself to the distal renal tubule and also on the secretion rate of aldosterone which enhances the exchange of potassium for sodium in this segment of the nephron. If the sodium intake is normal because the patient is eating normally and the potassium intake, augmented with fruit juices, is also normal, significant potassium depletion is uncommon. Cardiac failure is often accompanied by secondary hyperaldosteronism and hence a greater liability to potassium loss which may induce cardiac arrhythmias in patients taking digitalis preparations. About 40 per cent. of hypertensive patients taking benzthiadiazine diuretics daily show a fall in the serum potassium level but seldom below 3 mEq./litre. For this reason it seems wisest to give potassium supplements as a routine and these are certainly

indicated when: (1) the intake of potassium is low; (2) there is excessive potassium loss from diarrhœa; (3) digitalis preparations are being given; (4) there is cardiac failure with œdema; (5) the serum potassium level falls below 3.5 mEq./litre.

The amount of additional potassium chloride necessary may range from 1 to 4 g. daily and part of this may be incorporated in the diuretic tablet. Nobody, except pharmaceutical companies, likes compound tablets, but the severely hypertensive patient may require so many different drugs that for the sake of his comfort it is not unreasonable to use compound tablets containing the diuretic, reserpine and potassium chloride, although the amount of potassium may not always be sufficient to prevent potassium depletion (Bayliss and Fleming, 1960).

SUMMARY

Chlorothiazide and other benzthiadiazine diuretics are valuable adjuncts for maintaining a reduction in blood pressure. They achieve their effect by reducing the plasma and interstitial fluid volume, and find their chief use when combined with other antihypertensive agents.

Indications for using blood-pressure lowering drugs are discussed briefly. Treatment is indicated when there is evidence of hypertensive *disease*, as shown by disturbed structure or function of the retinal blood vessels (grades III or IV retinopathy), the heart or the kidneys. Treatment is also indicated in the absence of other signs or symptoms when the diastolic pressure is persistently greater than 110 to 120 mm. Hg, particularly in male patients aged 65 or less.

The main side-effect is potassium depletion which is likely to occur in certain defined circumstances. Supplements of potassium chloride are often necessary.

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THE DYING PATIENT

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PRACTICAL Medicine, like history, is more interested in the trend of events than in the events themselves, and so a doctor's interest in a dying patient is likely to be historical rather than philosophical.

AN END OR A BEGINNING

The question that should arise in his mind, as he sits by the death-bed, is: 'Should I regard this as an end or a beginning?' If it is an end there is nothing to be done but to ensure, so far as possible, that it is a comfortable one; but if it is a beginning there may be a great deal to do in preparation for the journey onwards. This is really the question of sedation; should we sit down and submit, or should we stand up and face it out together? It is here that history is helpful. There is a school of historians that maintains that man is born an ever-living spirit, that he is made in the Image of God, and that he partakes in some degree of the divinity of Jesus. This doctrine is so firmly established amongst intelligent people, and it answers so many questions, that, if only *faute de mieux*, it deserves to be accepted as, at the least, a working hypothesis.

If death were merely 'the ugly fact that nature has to hide' the treatment of dying would be very simple, for there are many ways of compelling sleep. But, so simple a solution of the Mystery of death satisfies nobody, for it begs every question that Reason persistently asks about the purpose of living, and cannot allay the dread of something after death that haunts man throughout his mortal life. The Christian Church answers the question with complete confidence, and without equivocation: 'Death is the gateway to which the whole of earthly life leads, through which we pass to whatever God purposes for us in Eternity'. This means that life has no beginning and no ending, it merely has phases. Earthly life is a phase of probation, so 'the better the end thereof than the beginning'. Death marks the end of this phase, and so, like a twenty-first birthday, it is a time for both tears and joy. Tears for the parents who are losing a child, and joy for the heir who has attained his majority. In what I am going to say I shall assume that this definition is accepted.

'A GODLY DEATH'

If the word 'euthanasia' had not been appropriated by those who believe in legalized suicide, it would have been a very suitable title for my dissertation for it literally means 'a good death', which gives in a word the target we should aim at in our care of the dying. It seems that this word was coined in the seventeenth century, perhaps suggested by Donne's 'Biathanatos' (a violent death), published in 1640. This is the title of 'A Declaration of that paradoxe, or thesis, that self-homicide is not so naturally sin that it may

never be otherwise', which John Hayward refers to as 'a curious and ingenious piece of casuistry'. 'Good' has many shades of meaning, and we must select the most objective of these. Bishop Gore, in his Gifford Lectures 1929-30, says that goodness, beauty, and truth, are different aspects of the mind and character of God. If we accept goodness as synonymous with godliness, our target is 'A Godly Death'. It is not a doctor's business to proselytize, but it is his business to know and use the full range of his patient's resources, and we can assume, *ex hypothesi*, that there is no such thing as an utterly godless person.

Doctors who appreciate the spiritual significance of death will agree that there is something pitifully inadequate in the conventional attitude of the medical profession to dying patients. There are various excuses for this, but here I am only concerned with principle. My contention is that this attitude is defeatist when it should be defiant, for death defied reveals, as nothing else can do, the dignity and power of man's unconquerable soul. My own experience is largely confined to hospitals, where the normal procedure has been described by an experienced physician as follows:—

'When there is no longer any hope of recovery, but plans have been made for nursing and the relief of symptoms, there is an art in allowing the relatives to take charge while the doctor recedes into a more secondary position'.

The doctor retires when the patient may need him most. He summons the relatives, tells them there is no more he can do, then washes his hands and retires. An attitude so reminiscent of Pontius Pilate when he was manœuvred into a false position by importunate Jews. Although he knew what justice demanded he could not face up to the awkwardness of seeing that it was done.

It is not quite the same in general practice, for the family doctor is usually a personal friend, but I would suggest that he, too, usually succumbs to the plausible assumption that there really is very little that he can do. Dying, he might argue, is a process of disintegration, outside the range of a healer. I know quite well that many doctors do not feel quite so helpless.

Dr. Hugh Barber (1959) tells of a wise old woman who was leaving hospital for a village where there were two doctors. Before she left for home she insisted on being told whether she was likely to recover, for if so she would choose one of the doctors, but if she were going to die she would choose the other.

It is always illuminating to see ourselves as our patients see us. This incident shows up two things about doctors: their division into those who accept responsibility for the health of the whole person, and those who will only accept the care of the body. It also shows the magic of the beloved doctor's visit. The kind of magic, of course, of which he himself is unaware.

Only those who have suffered from serious illness, and have been blessed in their doctor, can fully appreciate what this magic is. It is real magic, for it does not depend only on professional skill, or on personal charm. I believe there is always in it some reflected glory. Whether he knows it or not, a doctor who lives up to the ideals of his profession has in him something of a priest. The idea of wholeness is woven into the very fabric of Medicine, it crops up in various forms: the doctor's integrity—Hippocratic holiness—

Sherrington's integration—the word 'healing' itself. To complete the list, I am tempted to add the word 'catholic', from the greek '*kath holon*', according to the whole. All these have the same connotation of wholeness.

THE WANING BODY AND THE WAXING SOUL

It was the great achievement of the Archbishops' Commission on the Church's Ministry of Healing that it established as orthodox teaching that man is a unity of body, mind, and spirit; and it defined healing as 'the enabling of a man to function as a whole, in accordance with God's will for him'. Unless we accept this definition we are likely to get landed in hopeless confusion. 'Healing', like 'glory' in Humpty Dumpty's famous aphorism, is taken to mean 'just what I choose it to mean, no more and no less'. And so it has come about that the Church's ministry of healing is confused with necromancy. When a person is dying we need to rearrange the order of values in this formula. So far as the body is concerned healing has gone into reverse, while the soul unfolds like a chrysalis as it changes into a more perfect form. 'Ay, marry, now my soul hath more elbow room' says Shakespeare's dying King John. With a waning body and a waxing soul concern for things temporal becomes subordinate to the supremacy of the eternal.

The process of dying is a mystery. We profess to know something about why people die, but we know nothing about how they proceed to do so. It is not essentially dependent on physical disease, for a perfectly healthy native of Africa will proceed to die at the behest of a witch-doctor (Kaigh, 1947), and in a considerable number of post-mortem examinations the immediate cause of death is obscure. As a speculative proposition, the ordinary death certificate, if its real value could be assessed actuarially, would, I believe, compare very unfavourably at Lloyd's, with the Apostle's Creed. Yet dying is a specific process, with recognizable clinical features. It is a process of functional disintegration, but, so far as the mind is concerned, it does not follow the law of dissolution, expounded by Hughlings Jackson, according to which the highest level of intelligence should fail first. In dying, uncomplicated by mental disease or drugging, the mind may be clear to the end. Napoleon died on May 5, 1821, 'during the second half of the month of April, although his mind was still remarkably clear, his physical strength was ebbing fast' (Kemble, 1959). There is often a faraway look in the eyes which suggests greater insight. Trivial concerns no longer bother the burgeoning soul. Monica, mother of St. Augustine, before she was dying, gave precise directions about the disposal of her body after death, she was to lie alongside her husband; but when she was dying she cancelled these instructions, saying: 'Lay my body where you will, let no care thereof disquiet you'.

'THE PERSON BEHIND THE PERSONAGE'

Because he feels out of his element, a doctor's attitude to his dying patient is more often like that of a privileged onlooker, than that of a pilot. He approaches the bedside with diffidence and some awe, almost, I might say, with an awkward genuflection; and if he is bold enough to engage in conversation

he limits it to small-talk, studiously avoiding all reference to death. The kind of attitude that Matthew Arnold condemned in memorable verse:

> Spare me the whispering, crowded room,
> The friends who come and gape and go,
> The ceremonious air of gloom—
> All, which makes death a hideous show.

We are too apt to regard a dying person as already partially beatified, whereas, I am sure, one thing to be wished for is to be treated as an ordinary mortal. Personality does not change; during life it becomes overlaid with acquired characteristics, but 'the person behind the personage' is the same yesterday, today, and forever. As ageing and dying proceed the person is revealed, and we become as children again. This revelation of the person was quaintly shown in the last words of Ronald Knox, as recorded by Evelyn Waugh.

Just before he lapsed into the final coma he was asked if he would like to have read to him a portion from his new translation of the Bible. He answered 'No', and then, after a long pause, in which he seemed to have lapsed again into unconsciousness, there came from the death-bed, just audibly, in the idiom of his youth: 'Awfully jolly of you to suggest it, though'. These were his last words.

THE FEAR OF DEATH

I must now consider those two bugbears of humanity: the fear of death and the agony of dying. Fear of death and the pleasures of procreation are instinctive in all animals. They are relics of a time when the course of evolution depended upon survival and fertility. Neither instinct is quite appropriate to civilized man, whose dominion over nature has come to depend more and more upon fertility of mind, and less and less on generation, and whose idea of survival was extended for Christians beyond Time to Eternity, by the Resurrection. And so desire has become merged in love, and fear of death, like the fear of God, has acquired a reverential quality. Fear is rarely seen in dying patients, however much they may have dreaded death during their lives. Like the appearance of a distant hill to a traveller, fear recedes as death approaches. Although celebrated instances are sometimes exceptional, if they are well documented they deserve a place in our corpus of experience. I suppose no life has been better documented than that of Samuel Johnson; there can be little that we do not know of his intimate thoughts on every kind of occasion, and they are notable for their wisdom.

Right up to the last few months of his life he was afraid of death. He died in December 1784. In February of that year he wrote to Boswell 'I am extremely afraid of dying', but a few months later, when he knew that he was dying, his doctor reported: 'All his fears were calmed, and absorbed by the prevalence of his faith and trust in the merits and propitiation of Jesus Christ'; Boswell significantly added 'and Dr. Brocklesby could not be suspected of fanaticism'.

Fear of the unfamiliar is instinctive in infants, but it should be mastered in the course of a normal, healthy childhood. The fact that so often it is not, is due to faulty adjustment to reality. The fault may be in the person or his circumstances, usually in both, but it is a fault that admits of correction. Those who are familiar with Pavlovian principles will understand this. They

may, too, remember a famous experiment of the Pavlov School, in which fear was converted to pleasure by the superposition of a powerful food reflex, exalted by hunger, on a weaker one, conditioned by pain (Pavlov, 1941). It is said that when Professor Sherrington was shown this experiment by Pavlov, he exclaimed: 'Now I can understand the joy of the Christian martyrs when they were led into the arena to be devoured by wild beasts'. Had St. Paul been in Sherrington's place he might have evinced even greater emotion at seeing one who was acclaimed by his compatriots as a militant materialist, demonstrate to him how love can cast out fear.

THE AGONY OF DYING

We must distinguish the so-called agony of dying from the pain of the disease. 'Agony' is, unfortunately, another word of many meanings, ranging from an 'agony of pain' to 'an agony of pleasure', a more normal meaning is 'an agony of doubt'. Agony is a suffering and not a pain. The two conditions are essentially different. Pain is a feeling, like touch, mediated by a specialized system of nerves, which is an integral part of the structure of the body, and a vital link in its armour. Suffering is a state of mind that may be induced by pain, but there the relationship ends: the intensity of the suffering is not commensurate with the pain that induces it.

An experiment of Sir Joseph Barcroft, performed on himself, throws much light on the nature of the 'agony of dying', though it was not intended for this purpose (Barcroft, 1934). He was studying the effect of extreme cold on the thermostatic resources of the body. He exposed himself in a refrigerating room, and recorded his experiences as follows:—

> 'As I lay, naked, in the cold room at Woods Hill I had been shivering, and my limbs had flexed in a sort of effort to huddle up, and I had been very conscious of the cold. Then a moment came when I stretched out my legs and the sense of cold passed away to be succeeded by a beautiful feeling of warmth; the word "bask" most fitly describes my condition, I was basking in the cold. What had happened, I suppose, was that my nervous system had given up the fight, that the vasoconstriction had passed from my skin, and that the blood returning thither gave that sensation of warmth that one feels when one goes from a cold-storage room into the ordinary air. I suppose, too, that had the experiment not ended at that point, my temperature would have fallen rapidly, and that I was on the verge of the condition of travellers when they go to sleep in extreme cold never to wake again'.

He was in fact, on the verge of dying. The reactions he recalls are all to be explained as the attempt of the body to maintain the temperature of the blood at its normal level. The huddling up to reduce heat loss, the shivering to increase heat production, and the discomfort to warn him of his perilous plight. When the overwrought body abandoned the struggle, all suffering ceased with a blissful sense of release. Anything that encroaches on the integrity of the body is resented, and this resentment is expressed as distress of some kind.

In the light of this experiment it is clear that the so-called agony of dying is really the culmination of the agony of living, it occurred before the struggle was over, before dying had begun. This reminds us that the Agony of Jesus was in Gethsemane, not on the Cross. The approach to death may be

horribly painful, but the pain is in the disease, not in the dying; and the ending may be a hideous show, but the show is not visible to the patient, and the horror more apparent then real. The distorted features and convulsive movements are phenomena of release, due to withdrawal of the restraining influence of higher centres over the powerful reflex mechanism below, but this withdrawal only occurs when consciousness is in abeyance. The so-called agony of dying is a myth, wrongly interpreted. Like all myths it is truth adorned by imagination to appeal to primitive mind. To fit the importance of death exaggerated language is excusable. Like the lurid headlines of the Press it attracts attention to a momentous occasion, but experiment shows that the 'agony' is really a product of living, not of dying.

'I WILL TAKE NO MORE PHYSIC'

'We shall never understand the beneficial effects of a poison unless we first consider the havoc it can wreak'. So says Gustav Schenk in the opening sentence of his fascinating 'Book of Poisons' (1956). Doctors who practise self-examination would do well to include in this exercise the habit of regarding themselves in the role of poisoner, for all the powerful drugs they habitually use are poisons. It is reasonable to suppose that the alkaloids of opium were designed for man's use, for I believe that it has never been shown that their pain-relieving property is of use to the poppy; but, like all good things, they have the defects of their qualities. Morphia and its kind are given for relieving pain, but even small doses have a subtle effect on the mind. By bemusing the Critic in the Cortex, judgment is debased, and imagination exalted, which induces a fanciful, couldn't-care-less attitude to reality. Amongst its other evil effects are depression of the respiratory centre causing Cheyne-Stokes breathing, nausea, central vomiting, and bowel dysfunction; these distresses may add considerably to the unhappiness of the last few days or weeks of life. There are many potent drugs for the local control of visceral function when central control is failing, nikethamide for respiratory failure, the various hormones of the adrenal gland for over-reactions and metabolic disorders, mercurial diuretics for draining flooded areas, and a host of less powerful drugs for symptomatic treatment that discreetly used will contribute to comfort, without resort to sedation.

Opiates should be reserved for the pain of the disease; sometimes it is necessary to give them boldly, not counting the cost, but when we do this we should feel in our hearts that it is an admission of failure to achieve the good end at which we had aimed. Sometimes the patient will decide the matter for himself. When Dr. Johnson was told that he was dying he said to his doctor: 'Then I will take no more physic, not even my opiates, for I have prayed that I may render up my soul to God unclouded'.

THE DIGNITY OF DEATH

I would suggest that the care of the dying consists essentially in preserving the dignity of death. It is at a death-bed that the ministrations of the Church

and Medicine are obviously complementary, though they are working on different planes. The doctor, because of his knowledge of the ways of the body, and his unique responsibility as curator of the person, should be in control. It might be argued that the Church is the senior service and so it is to the clergy that this privilege belongs, but it is the pilot and not the senior officer who controls navigation while a ship is crossing the bar. Dying is surely as worthy of dignity as, shall I say, a Passing Out Parade at a military college; sometimes, indeed, it is as worthy as a Coronation. The ceremonial, proper to such solemn occasions is not merely symbolic, it has profound intrinsic value of its own. The Grace of a Crowning is not in the pomp and panoply of Majesty, but in the simple anointing with oil. 'Not all the water in the rough, rude sea can wash the balm off an anointed King'. I end with some extracts from John Gore's account of the death of King George V: a classic example of the dignity of dying.

'The King had carried on to the limit of his physical powers and when death came he was at the end of his road. . . . He died, as he had lived, close to the people of his Empire, and it seemed that his death-bed was brought within reach of every home in the Commonwealth. . . . On Monday, 20th January, the news was much graver and the Council arrived. . . . Before they came the Archbishop of Canterbury had given him his blessing and thereafter the King tried to repeat the Lord's Prayer, but sleep had closed down on his mind. . . .

'When the Council arrived they found him sitting in a chair in his dressing gown, with a table before him. He greeted them with a nod and his familiar smile. The formal business was quickly done, setting up the necessary Council of State. The Lord President read the Proceedings and in a firm voice the King said "I approve". But by now his right hand had lost power and he could not sign the order . . . several minutes elapsed while he strove with either hand to shape the letters and the pen turned between his fingers. As he strove, looking up at the Council he said "I am sorry to keep you waiting, Gentlemen, but I find it difficult to concentrate. . . ." At last he achieved two barely recognizable marks. Then he dismissed them with his charming smile. . . .

'That night the Royal Family dined alone. During the Household dinner they sent in to Lord Dawson for the wording of the nine o'clock bulletin. Lord Dawson consulted Lord Wigram who sat next to him and said to the company "I think the time is past for details". Then it was that he wrote on the back of a card, which Lord Wigram handed to him, the doctor's last and most beautifully worded message: "The King's life is moving peacefully towards its close".

'This message was heard at regular intervals, during that dark and bitter night, all over Britain and the Empire; solemn, inexorable, peaceful, as the tolling of a passing bell'.

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Based on an address to the Oxford Clerico-Medical Group on May 16, 1960.

THE TREATMENT OF ACNE VULGARIS WITH GRADED ABRASIVE CREAMS

REPORT OF A CLINICAL TRIAL

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Acne vulgaris was described by Borrie (1956) as 'a chronic inflammatory skin disease in which excessive sebum, secreted by overactive sebaceous glands, is unable to escape from the hair follicles owing to hyperkeratotic plugging of their orifices'. It is therefore logical to assume that the aim of treatment should be to unblock the pilo-sebaceous follicles, thus allowing the retained sebum to escape and permitting the sebaceous glands to return to normal size and activity.

Since, in the majority of cases, acne vulgaris is a self-limiting disease, it is important that any topical application should be not only effective, but also harmless and cosmetically acceptable. This latter requirement seems to us to be of particular importance, since a messy ointment, however effective, is rarely used consistently by the patient. On theoretical grounds, 'brasivol' seemed to fulfil these conditions and to merit evaluation. It is described as containing fused synthetic aluminium oxide (the abrasive) in a soap-detergent base with 1 per cent. hexachlorophane—and is available in three grades to provide various degrees of abrasion.

Group	Clear	Improved	No improvement	Totals
Grade 1 (comedones only)	3	3	0	6
Grade 2 (comedones and papules)	11	17	4	36
Grade 3 (comedones and pustules)	8	12	2	22
Grade 4 (cystic acne)	3	5	2	11
Totals	25	37	8	75

Table I.—Results from the use of abrasive creams in acne vulgaris.

SCOPE OF INVESTIGATION

Every patient with acne vulgaris seen in the outpatient department was treated with the preparation under test. There was no selection of cases, all patients receiving the same treatment regardless of the severity or duration

of their acne. In all, 75 patients (34 male, 41 female) were treated for periods of up to nine months. Their ages ranged from one child of eight to a woman of fifty, the maximal incidence being in the 15-20 age-group.

Although a 'blind trial' would obviously have been desirable, the very nature of the preparation prevented the use of a non-abrasive placebo without the patient's knowledge. We thought also of asking each patient to use the cream on one-half of the affected area only, but when the preparation proved effective, patients promptly used it on the whole area. On the first visit, each patient was examined, photographed, and the degree of severity of the acne assessed according to the following grouping:—

Grade 1 (6 cases)—mildest form having comedones only
Grade 2 (36 ,,)—comedones and papules
Grade 3 (22 ,,)—comedones and pustules
Grade 4 (11 ,,)—severest form: cystic acne

Every patient started treatment with the fine grade of 'brasivol' (No. 1) and was instructed to rub the cream on to all the affected areas for about half a minute, to leave it on until it became powdery (five to six minutes), and then to rinse it off with cold water. This routine was to be carried out night and morning, and if possible, at mid-day also. The importance of not squeezing spots and thereby producing secondary infection with scarring was explained.

No other treatment was employed in these patients, no dietary restrictions were imposed, nor was the use of cosmetics forbidden in females although they were advised to discard the powder-puff in favour of using a clean piece of cotton-wool each time powder was applied.

The patient was then seen at intervals of approximately three weeks (the average time taken to use one jar of the cream), and progress assessed. When response to the fine-grade paste was observed, the next degree of abrasive was prescribed.

RESULTS

The results are summarized in table I. Of the 75 patients studied, 25 were cleared completely after six to twelve weeks and required no further treatment. A further 37 showed a very marked improvement in that they had far fewer spots, the eruption occurred less often, and the spots were much reduced in size, and lasted only one or two days instead of four to five. Eight patients showed doubtful or no improvement. Two stopped treatment because it was not helping them, but no patient was made worse. Five patients, four in grade 2 and one in grade 4, were lost sight of.

Two patients had to interrupt their treatment temporarily, because they developed impetigo. One of these, a young man with severe cystic acne expressed a wish to return to 'brasivol' when the infection had been cleared, as he said it 'kept the blackheads down'. Two fair-skinned, red-haired girls found that 'brasivol' at first produced irritation and erythema, but this dis-

appeared as treatment was continued. One young woman developed a mild erythematous eruption on her face, but was found to be keeping the paste on overnight. The rash cleared without further treatment when she removed the cream after five minutes as she had originally been instructed.

Six of the patients who cleared completely after using the abrasive cream relapsed when it was stopped. Reapplication of the preparation has controlled the condition again in all cases.

DISCUSSION

Since this trial extended over the period December to June, we thought it advisable to compare the results obtained during the winter months (December to March) with those obtained from March to June. There was no significant difference, and exposure to sunlight in the latter period was therefore not considered to be responsible for any improvement observed in patients treated during that time. Two cases of acne excoriée improved for about six weeks, but then broke down again. We would, however, agree with Saperstein (1960) that the psychological effect of applying treatment is beneficial in many cases, and replaces the picking and squeezing and minute inspection that otherwise tends to occur. It was interesting to observe that there was a family history of acne in all but one of the patients in grade 4, in 16 of those in grade 3, in 10 in grade 2, and in none in grade 1. One female patient who was somewhat hirsute was at first thought to be less so during 'brasivol' therapy. This observation, however, was later proved erroneous, the condition being actually neither improved nor worsened.

In our experience 'brasivol' is a valuable aid in the treatment of acne, and is acceptable to the patients.

SUMMARY

Seventy-five cases of acne vulgaris of varying severity and duration were treated with graded abrasive pastes for periods of up to nine months.

In 25, the condition cleared completely after six to twelve weeks' treatment; in a further 37 there was marked improvement; eight failed to respond.

Maintenance therapy is helpful and necessary as the tendency to acne remains.

Side-effects were minimal and no patient was made worse. Cosmetically, and consequently psychologically, the treatment seems beneficial; the vigorous rubbing in of the paste replaces the squeezing, picking and minute inspection.

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THE PROBLEM OF DENTAL PROSTHETICS FOR EXPECTANT AND NURSING MOTHERS

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MANY expectant mothers having their first medical examination are advised to have their teeth attended to before the baby is born. Unfortunately, when then seen by the dentist, complete or partial removal of the remaining teeth is often necessary. As the mother must be capable of accepting an adequate diet she must not be without teeth for any considerable time. Also she should not have to attend for serial dental appointments for the few weeks preceding, or following, the birth of the baby.

GENERAL PROCEDURE FOR TREATMENT

The mother has usually had her initial medical examination during the first sixteen weeks of pregnancy. If dental extractions are required it is advisable to have these teeth removed at sixteen to twenty weeks after the start of pregnancy, the risk of miscarriage between the fourth and sixth months being minimal. Local anæsthesia is preferable to general anæsthesia, the latter having the possible attendant risk of anoxia. Immediate dentures could be inserted at this time but the strict attention that the patient must observe with such dentures might not be undertaken by the patient who has previously neglected her oral health.

The mother could well be left for twelve weeks following extractions, until the end of the seventh month, when normal routine denture procedures could be undertaken. This will allow her to gain confidence with dentures and allow for adequate nutrition for the periods immediately before and after the birth of her child. If the removal of the teeth is delayed until the sixth month, post-immediate dentures could be made some four to six weeks later, following the period of rapid alveolar bone resorption. This healing period could be encouraged by alveolar bone surgery at the time of the extractions, with the aim of obtaining good contouring of the alveolar ridges during the healing process. If the patient is not seen before the end of the sixth month, immediate dentures must be considered. These should last the patient satisfactorily through the birth period, and early relining of the dentures should not be required. For this reason immediate dentures of the flanged type employing a septal crush at the time of the extractions are to be preferred to socket-fit dentures. Of these alternative lines of treatment, the first, where the mother waits some twelve weeks after extractions followed by routine prosthetic procedures, is generally the method of choice on the basis of its simplicity and lack of complications.

Finally, I would stress the importance of close cooperation between doctor and dentist at the earliest possible date in the mother's pregnancy.

PREGNANCY IN THE DIABETIC

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A special clinic for the supervision of pregnancy in diabetic patients is held weekly in the University Unit of St. Mary's Hospital by the Professor of Obstetrics (Professor W. I. C. Morris) and a member of the medical staff of the Manchester Royal Infirmary. The majority of such pregnancies referred to the hospital are supervised in this clinic. At each visit all patients are seen by both obstetrician and physician. This article is a review of cases supervised between March 1956 and August 1959 when all were seen by the author.

METHOD OF SUPERVISION

During this period, 62 pregnancies in 54 diabetic women were managed in the Unit. The patients were seen normally at fortnightly intervals, but weekly if thought necessary, and always weekly after the 30th week of pregnancy had been reached. Normally, admission to hospital was arranged about the 35th week and delivery was usually by induction or Cæsarean section about the 36th or 37th week.

When first seen all patients requiring insulin were put on two doses of soluble insulin daily, and the diet was adjusted to suit this regime. A small dose of protamine zinc insulin, 4 to 10 units, was combined with the evening dose of soluble insulin to prevent morning ketosis (Oakley, 1953) and it was often found that this improved the blood-sugar control also. The patients themselves were asked at each attendance whether their diets appeared satisfactory and, if necessary, they were sent to the dietetic department of the Manchester Royal Infirmary for adjustments to be made. About 40 per cent. of the calories were given as carbohydrate and, as two doses of soluble insulin were being given, about 25 per cent. of the calories were given at breakfast and 25 per cent. at the evening meal.

As St. Mary's is a busy hospital serving a large area, beds for inpatient treatment are precious and every effort was therefore made to manage the diabetic patients in the outpatient department so far as possible. In the majority of patients adequate control of the diabetes was easily achieved but a few required short-term admission to obtain good control. The aim was to keep the mid-morning blood sugar between 100 and 200 mg. per 100 ml., and, if possible, between 100 and 150 mg. per 100 ml. If admission to hospital was required, mid-afternoon blood-sugar levels were also estimated and often one about 20.00 hours. Dosage of insulin was adjusted to keep all these blood-sugar levels between 100 and 150 mg. per 100 ml. No reliance was placed on the results of urine testing for sugar as the renal threshold is often reduced in pregnancy (Joslin *et al.*, 1959d) and the patients were asked not to test their own urine while attending the clinic.

RESULTS

Maternal mortality.—There was one maternal death; this occurred from broncho-pneumonia as a result of a severe hypoglycæmic attack in the first trimester of pregnancy. The circumstances of this were not absolutely clear.

The patient was a long-standing diabetic who seemed quite familiar with her own management. She had attended the clinic once, when her diabetic control and general health were quite satisfactory. She defaulted next time and a postal request asking her to attend again was ignored, although subsequently she was known to have been alive at the time it was sent.

Abortions.—Loss of the fœtus before the 28th week of pregnancy occurred six times (9.7 per cent.). There was no obvious cause for this in any of the patients, but one had severe diabetic retinopathy though without evidence of any renal disease. Four occurred before the 12th week, one at 18 weeks and one at 24 weeks.

Viable fœtal loss.—Fifty-five patients reached the 28th week of pregnancy and in four of these, a stillbirth resulted (7.3 per cent.). Of the 51 live births, seven died, all within fourteen days, giving a neonatal death rate of 13.7 per cent. The total viable fœtal loss was 20 per cent.

PRE-ECLAMPTIC TOXÆMIA AND HYDRAMNIOS

(a) *Pre-eclamptic toxæmia.*—Criteria for the acceptance of a diagnosis of pre-eclamptic toxæmia are very variable, but it is necessary to keep to a strict definition if a true assessment of its frequency is to be made. Strict criteria have been laid down by Nelson (1955) whose definition is:—

'*Mild grade.*—With or without œdema, the blood pressure (diastolic) rises to 90 or more on two or more occasions separated by at least a day, or shows a definite or progressive pattern if the rise occurs in labour. The readings should not be so separated that a definite relationship cannot be inferred. This hypertension occurs in the absence of albuminuria'.

In the presence of hypertension so defined the presence of albuminuria raises the grading to severe.

Based on these criteria pre-eclamptic toxæmia occurred only once in the 62 pregnancies in this series. It was of mild grade and the blood pressure was never higher than 150/90 mm. Hg. It settled rapidly with rest. As the patient was a multipara, labour was induced surgically at 36 weeks. A live baby resulted which survived.

(b) *Hydramnios.*—The diagnosis of hydramnios was always made by the same observer (Professor Morris). Hydramnios occurred in 23 pregnancies (42 per cent.). In five of these a stillbirth or neonatal death resulted (21.7 per cent.); a figure barely worse than that for the whole series (20 per cent.).

MODES OF DELIVERY

Vaginal delivery.—Vaginal delivery occurred spontaneously or was induced in 15 pregnancies (27.3 per cent.). In four, labour was induced at 36 to 37 weeks because the patient had had one or more previous vaginal deliveries. All of these resulted in a live birth, but one baby aged 13 days died of staphylococcal broncho-pneumonia. In another a surgical induction was performed at 36 weeks instead of a Cæsarean section in a primipara, because the mother was aged eighteen years, unmarried and was emotionally

very unstable. Cæsarean section was thought to be unjustifiable. The baby was born alive but died, aged 20 hours, of atelectasis and hyaline membrane disease.

Vaginal delivery was allowed to occur spontaneously in four pregnancies in which an intra-uterine death was known to have taken place. No obvious cause for the intra-uterine death was apparent in three; in the fourth it had taken place during a severe episode of diabetic ketosis during an acute attack of pyelonephritis. Two further pregnancies were allowed to go to term because the mothers were both very mild diabetics requiring no insulin, and the babies did not appear to be growing very large (birth weights: 5 pounds 12 ounces [2.6 kg.] and 8 pounds 7 ounces [3.8 kg.]). In the remaining four pregnancies, labour began spontaneously at or before 36 weeks. One began at 28 weeks; the baby was born alive, but died aged 2 hours; there was no obvious cause of death at necropsy. In two, labour began at 32 weeks; one baby was quite satisfactory, but the other died of kernicterus aged six days. In the fourth, labour began at 36 weeks; the baby was healthy and survived.

Cæsarean section.—The remaining forty deliveries (72.7 per cent.) were all managed by Cæsarean section at 36 to 37 weeks with the loss of only three neonates with hyaline membrane disease (7.5 per cent.).

DIET AND INSULIN

If the pregnancies ending in abortion and the patient who died in early pregnancy are excluded, this leaves 55 pregnancies reaching at least 28 weeks. Four pregnancies were in very mild diabetics who were controlled by diet alone and no insulin. No changes in the diet were required during any of these pregnancies. In the 51 pregnancies in which insulin and diet were required, eight required no change in either diet or insulin, and one required an increase in diet of 500 calories, but no increase in insulin (in fact the requirements dropped by 12 units of insulin in the first trimester, thereafter returning to the previous level). Among the remaining 42 pregnancies in only 20 was an increase in calories required, the increase varying from 200 to 600 calories. The total daily requirements at the end of pregnancy ranged from 1,800 to 2,700 calories. All 42 patients, however, required an increase in insulin. In 10 cases the insulin requirement was more than doubled; in two pregnancies the needs were tripled and increased more than eightfold in two. Diabetes developed during the course of one pregnancy and 70 units of insulin were required: six weeks following delivery no more insulin was required and the blood sugar was normal. Following delivery the insulin requirements of most cases fell to the level required before pregnancy. In one case, no insulin was required initially, and 36 units daily before delivery, and this dose was still needed following delivery.

HYPOGLYCÆMIA AND KETOSIS

Mild *hypoglycæmic attacks* were quite frequent, but only two were severe. In the first patient, hospital admission was arranged to establish control,

and the second was the patient who had defaulted and died from bronchopneumonia following the incident.

Ketosis was often present but was of mild degree except once when it was associated with an attack of acute pyelonephritis. Intra-uterine death occurred during this episode. In the next pregnancy this patient's ketosis was easily controlled by giving three doses of soluble insulin daily.

CONGENITAL ABNORMALITIES OF THE FŒTUS

Necropsies were performed on the four stillbirths and seven neonates which died. In one neonate there was found to be premature closure of the fontanelles. Apart from this the only other abnormalities found were patency of the ductus arteriosus and foramen ovale in seven cases, which can hardly be regarded as abnormal, and in one there was a single central pelvic kidney with one ureter in the midline.

Four of the 44 babies who survived were found to have congenital abnormalities. One had an extra digit, a hemivertebra and an undescended testis at the age of 13 months; another hypospadias, an angioma and depressed sternum; the third, 13 ribs and hemivertebræ, and the last a congenital ptosis. Leaving out those babies with a patent ductus arteriosus and patent foramen ovale, all diagnosed by necropsy, the incidence of congenital abnormalities in the series was 10.9 per cent.

DISCUSSION

The present series consists of 62 pregnancies in 54 diabetic women; 55 pregnancies reached at least 28 weeks' gestation and resulted in a stillbirth plus neonatal death rate of 20 per cent.; 10.9 per cent. of the 55 fœtuses had definite congenital abnormalities.

The viable fœtal loss in diabetic pregnancies has always been high. In this country, even in places where a special interest has been taken in the problem, until recently it was always well over 20 per cent.: 27 to 28 per cent. (Oakley, 1953), and 25 per cent. in the 136 pregnancies in the Medical Research Council's hormone trial (1955). It appears, therefore, that in the ordinary way results much better than this are virtually unobtainable, although it is of interest to note that by admitting the mothers to hospital for rest and stabilization at 32 weeks, Peel and Oakley have reduced the total viable fœtal loss to 18.9 per cent. (Brudenell, 1959), and Brandstrup and his colleagues (1954) had previously claimed a reduction to 10 per cent. by the same method. In the Medical Research Council's hormone trial (1955) no improvement resulted from the use of hormone therapy despite the reduction in total viable fœtal loss to 10 per cent. claimed as a result of such therapy in the United States (Nelson, Gillespie and White, 1953). There should be no risk to the mother's life attributable to the diabetes provided that there is proper supervision, as pointed out by Oakley (1953).

Toxæmia of pregnancy is usually regarded as a common complication of diabetic pregnancy (Peel and Oakley, 1949) but such has not been borne out by the present series in which only one example was seen in all 62

pregnancies—less than 2 per cent. On the other hand, hydramnios was definitely quite common, occurring in 37 per cent. of the series, but this did not appear to have any significant adverse effect on the total viable fœtal loss in the present series although it has been noted to have an adverse effect in other series (Peel and Oakley, 1949).

Peel (1955) states that there is no convincing evidence that the abortion rate is higher in diabetics than in others. In the Medical Research Council's hormone trial the rate was between 7 and 8 per cent. and in the present series it was 9.7 per cent. The difficulty in making comparisons here is knowing what is the usual abortion rate in non-diabetics, but it is generally accepted as being about 10 per cent. (Jeffcoate, 1957; Joslin *et al.*, 1959a).

It was found quite satisfactory to control the diets by allowing each patient to decide whether she needed more or less food and adjusting the calories as required. The same proportion of carbohydrate was kept (40 per cent. of the calories). There were no grossly overweight patients. Ketosis was not usually any real problem; it was only troublesome in the patient already mentioned who required three doses of soluble insulin daily during the last few weeks of her second pregnancy.

Only one patient was found to require less insulin during pregnancy in the present series and this was only during the first trimester. This is a well-recognized fact (Jones and Providence, 1956; Joslin, *et al.*, 1959b; Lawrence and Oakley, 1942). An appreciable number in the series (23.6 per cent.), however, required no increase at all throughout pregnancy. Lawrence and Oakley (1942) record a patient who needed 15 units of insulin before the onset of pregnancy, 66 units at the end of pregnancy and none following delivery. She 'still required no insulin when seen long after delivery'. One similar patient occurred in this series who was a diabetic of twelve months' standing taking 20 units of protamine zinc insulin daily.

At the end of pregnancy she required 24 units of soluble insulin twice daily and this amount was still necessary following delivery. After discharge home, however, she stopped taking any insulin and diet and successfully negotiated a second pregnancy a year later without taking any diet or insulin and without ever having a blood-sugar level higher than 150 mg. per 100 ml. The delivery was a normal one and the baby, who weighed 5 pounds 12 ounces (2.6 kg.), appeared quite normal and survived.

There appears to be conclusive evidence that the incidence of congenital abnormalities is higher in the offspring of diabetic mothers, the expected incidence in normal pregnancies being 1.8 per cent. (Joslin *et al.*, 1959c). It has been suggested that lethal abnormalities are commoner but evidence for this is scanty (Miller, 1956). The apparent increase may be partly artificial due to the fact that congenital abnormalities are likely to be sought by necropsy in every diabetic pregnancy in which a stillbirth or neonatal death has occurred.

SUMMARY

A series of 62 diabetic pregnancies is reviewed in 54 women, representing three-and-a-half years' work in the joint diabetic clinic of the University Unit at St. Mary's Hospital, Manchester.

As usual, a high stillbirth plus neonatal death rate was found (20 per cent.). Contrary to the accepted belief, toxæmia of pregnancy was not a common finding (less than 2 per cent.) but hydramnios was frequent (37 per cent.), although not significantly affecting the viable fœtal death rate adversely. The standard mode of delivery was Cæsarean section at 36 to 37 weeks' gestation. This was applied in 40 pregnancies with the loss of three neonates from hyaline membrane disease (7.5 per cent.).

The calorific value of the diet was adjusted mainly according to the patient's appetite, 40 per cent. of the calories being given in the form of carbohydrate. Insulin was given as two doses of the soluble variety and usually a small dose of protamine zinc insulin was combined with the evening dose to smooth blood-sugar control and prevent morning ketosis.

Ketosis and hypoglycæmia were not usually problems of any magnitude and were avoidable with the adequate supervision and cooperation of the patients.

The maternal mortality due to the diabetes should be nil.

There was a high incidence of congenital abnormalities (10.9 per cent.) in this small series, but not of lethal ones. Evidence in the literature regarding the incidence of the latter is inconclusive.

The results indicate the value of regular outpatient attendances to see both obstetrician and physician, in order to avoid occasional accidents and to ensure that the best time be chosen for hospital admission and delivery. Even so, the total viable fœtal loss is usually 20 to 25 per cent., but there is some evidence that improved results occur when the mothers are admitted at 32 weeks for rest and stabilization.

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THE JAMES MACKENZIE LECTURE

THE MEDICAL ADVISER*

By LINDSEY W. BATTEN, M.B., M.R.C.P.
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NO-ONE who is privileged to deliver this lecture can refrain from first paying his tribute to the memory of the man in whose honour the lectureship was founded—Sir James Mackenzie. Superficially regarded, here was a man who climbed young ambition's ladder from general practice in an industrial town to the eminence of consulting cardiology in the Metropolis, with financial success, knighthood and international fame. But it is clear from his own writings that the inner truth is otherwise. Far from 'spurning the base degrees by which he had ascended' he writes after eleven years on the plateau as one still on the ladder, pointing out that only as a general practitioner could he have made the observations which threw such new light on the workings and disorders of the heart, and urging that the same must needs apply in a far wider field.

> 'Only the general practitioner', he writes, 'has the opportunity for finding out the significance of the various signs, a knowledge which is absolutely essential to the investigation of disease, as well as to the rational practice of medicine'.

From this and many other relevant passages, and from his deliberate forsaking of London and cardiology for the investigation of symptoms in the company of general practitioners at St. Andrew's, may one not deduce that consulting cardiology was no more than a phase in the life of a great general practitioner, as was London in the life of a great Scotsman, and that neither cardiology nor London satisfied his soul?

I think we may also conclude that in this College of ours, more, even, than in cardiology, he 'is mighty yet, his spirit walks abroad'. Much of his teaching concerning the heart—the predominant importance of symptoms over signs and instrumental recordings in the estimating of cardiac efficiency, for example—has been very imperfectly absorbed but the College, with its emphasis on education for and research in general practice, directly fulfils and expresses some of his most cherished aspirations. This is the more remarkable because, as I understand, the fathers and founders of the College were not steeped in his writings when they laid the first stones, yet their minds jumped with his. I am sure if he were here with us he would accept with pride the presidency the College would proudly offer.

THE FRAGMENTATION OF MEDICINE

I am less certain that he would be pleased with the present state of general

* The seventh James Mackenzie Lecture, delivered before the College of General Practitioners on November 19, 1960.

practice. He would find its scope in many ways sadly shrunken. The fragmentation of medicine, which distressed him, has continued; recording machines and laboratory tests, which he distrusted, have multiplied, and the tendency, which he deplored, to rely too much on them, too little on our unaided senses, has certainly not diminished. Medicine has not been simplified, as he hoped it would be. With the help of remedies put into our hands by others we can save many patients from death who in his day would have died and can keep at home under our care many we must then have sent to hospital, but our skill in using our five senses for diagnosis and our hands in treatment is almost certainly less than was our fathers' and I doubt whether our power of prognosis, on which he laid such stress, has appreciably increased. Many regret these tendencies and here and there they may perhaps be countered but it is hard to see how they can be put into reverse and, as we all know, there be many that say the individual general practitioner, if not the group or team, has had his day and fulfilled his function. He is in a state of progressive atrophy, regrettable, perhaps, but quite inevitable. He must go.

I do not wish to argue the case for the general practitioner when engaged in his traditional pursuits of diagnosis, prognosis and treatment, or to forecast his future, but to concern myself with another of his manifestations —that of *adviser:* not an adviser to collective bodies—the Treasury, an army, battalion, factory, borough or school; the field would be far too wide; but to single individuals or at most to families. My subject is the personal or family doctor consulted—even spoken of—as *adviser*. I think the subject is worth talking about because it is too little recognized in pre- and post-graduate medical education, by every sort of planner, by the State, the public and even by doctors themselves, especially when engaged, as so many of us now are, in devising or revising schemes for the supply of medical services. This neglect is nothing new and would matter less if organizing and planning were less in fashion but as they are much in fashion it matters much.

RETROSPECT

The doctors of my vintage had, I consider, on the whole, a very creditable medical education. I look back on it with far more gratitude than criticism and in many respects it might have been approved of even by that unsparing critic, Sir James. Physiology, for instance, was taught to me at my medical school not by a physiologist but by two practising physicians, of whom one became a neurologist and the other a notable general physician with a prophetic eye on Psyche and the endocrines. I am sure this was as it should be and that it was no accident that the teacher who got most anatomy into my unreceptive and unretentive head was not an anatomist but a surgeon. We were, in my view, well taught, and taught also with an eye to general practice. One or two of our consultant teachers had themselves been general practitioners and most of them met family doctors daily and knew both them and their problems well, but, for all that, they did not tell us that we should

be constantly asked for advice or teach us how to give it. Then as, I suspect, now, we had to find out for ourselves.

Yet this subject—advice and how to give it—could be taught by precept, example and practice. Why should it not be? One of our physicians (but I was not on his firm) did, I believe, do something of the kind for I remember hearing him dictate, for the benefit of his clerks and housemen, a letter to an imaginary patient either answering a question or giving advice, but even that may well have been directed to details of treatment and I fancy his colleagues on the senior staff might have frowned slightly, had they been present—as at a breach of decorum. Taken all in all, however, we were not taught the art of advising or urged to look forward to it as an important part of practice; yet we were not long in practice before we found it so and I propose to try and indicate something of its scope—the kinds of question or situation which demand it, the kinds of answer the medical adviser may give.

PREMARITAL ADVICE

I shall begin with the lover, in the shape of a young man or woman intending to marry, or the engaged couple complete, coming to see the doctor, seeking, in current phrase, premarital advice. I shall make no attempt to cover the ground, which has been pretty thoroughly tilled by others, but I should like to say that the medical man has at least one advantage over the non-medical counsellor. He can lead off with a physical examination like that for life-insurance—searching, perhaps, but not highly charged with emotion—and whatever advice or counsel he has to give can spring unembarrassingly out of this examination. There are, of course—and quite rightly—other advisers available and the practitioner will not take it amiss if the son or daughter of the family decides, on this occasion, to go elsewhere.

On the other hand, there are certain problems on which he is pre-eminently qualified to give advice. Let us suppose, for instance, that in the course of examination it turns out that one of the couple has sugar in the urine and proves to be a diabetic. What now? We have, of course, considerable control over the disease but we cannot cure it and many of its 'side lines' are persistent, intractable, distressing and disabling. The young patient may well believe: 'It's all right now. There's insulin'. Alas! We know better. We know, too, that it is inheritable and is increasing amongst us—a 'side-effect' of insulin's life-prolonging power. I have heard a consulting physician suggest that diabetics should not have children, and an American writer on 'Medicine and Morals' who holds that babies have a right to be born free of what he calls a 'taint' would without doubt agree. Must our adviser tell these young people that if they venture on marriage they should keep it childless or even that they should not venture at all?

Let me say at once that this particular painful problem never came my way but if it had I would certainly have recalled a talented young painter, diabetic before there was insulin and well knowing his fate, married to a

singularly lovely girl, who also knew. He died but left with me, then a medical student, the brightest picture of young married love I ever looked upon.

'DOCTOR'S ORDERS'

It is well for the medical adviser that his job is to advise, not to give orders or pass judgment. I admit to wincing at the expression 'doctor's orders'. In the case stated and in many parallel cases his duty seems to me clear enough. It is to put the truth, the relevant facts, before those consulting him, not confusing theory or surmise with fact, or probabilities with certainties, or letting it be thought that medical considerations must outweigh others, and then, quite firmly, put the decision where it belongs—with them. If pressed hard to say what he would do in the like case he should give an honest answer but still make it clear that he speaks only for himself or, at most, gives the answer of his profession. There can be no question of bringing tables of stone down from the mount. I am equally sorry to hear: 'Of course he couldn't go against the doctor *but* . . .' and 'He wouldn't do what the doctor told him *so* . . .'; even 'It was a good thing they obeyed the doctor' is not much better. What I like to hear is: 'So he told them everything about it and they talked it over and decided . . .'. That, I am quite sure, is how it should be, at least when ponderables and imponderables, things physical and things metaphysical, things seen and things unseen must be weighed against each other. Personally I may hope our couple will risk it but it is not for me to tell them so. The adviser's advice is 'to think it over and decide'.

Let us leave advice before marriage, only noting that now and then a family doctor who knows one of the couple—or perhaps both—really well may be able to give advice on intercourse which few others are in a position to give and which can much increase their chances of 'living happily ever after'.

ANTENATAL CARE

Advice in pregnancy comes next and the personal medical adviser is at least as much needed in these days of antenatal clinics and books and pamphlets for expectant mothers as he was before they existed. Sometimes, no doubt, that splendid serenity of mind and conscious well-being that set in about the third month may breed in the mother-to-be a fine contempt for the whole tribe of 'antenatallers'—especially if she has trod the path before—and carry her through to a happy issue with nothing more than the necessary physical checks on progress—which I am far from decrying. But there are other times when, having read the little books, listened to friends and attended clinics, the poor girl finds herself more and more confused. Must she really weigh weekly and is it quite fatal to get plump? How, precisely, does the fat-free diet mix with all that milk? Must she boil her breakfast egg while she fries her husband's? Are all the little tablets really necessary? What, exactly *is* the Rhesus factor and what *exactly* happens if . . . ? It is terribly hard to find the time for these contractings and relaxings, with the children and husband and flat and her mother not well just now. Must she really?

To whom shall she turn? Probably few here needed Professor Morris's quotations from patients to tell them what happens in clinics. We chuckled as we read our *Lancet* and thanked him for his courage and frankness.

'As you entered, the doctor was already reading your case-sheet and we were on and off the examination table in two shakes'.

'The midwives at the hospital all seem to have too much to do to bother with the odd person who wants to know "why, where and what" '.

Doubtless they not only *seem* but have indeed too much to do and all too often not only they but the medical staff at the hospital or clinic do not recognize it as part of the job to listen, explain and advise. Unless patients are the equivalent of René Clair's memorable little horses on the conveyor belt it is someone's job to do just that, to do it, too, for the 'odd person who wants to know', not for the many admirable persons who do *not* want to know but are content to trust the doctor and do what they are told. The answer is not the extension of broadcast medicine; it is the preservation and encouragement of the personal medical adviser. Only he—or she—can give this particular perplexed expectant mother the advice and comfort she needs and ought to have. Standardized advice is no good to her.

'INFANT WELFARE'

With or without the help she ought to have, however, she worries through and gives birth and immediately the trouble starts over again. Here, in the field of 'infant welfare' I feel, is almost a tragedy to be recorded—a Paradise lost, hard, though perhaps not impossible, to regain. Here is a province of advisory medicine which, more, perhaps, than any other, the seeker for and the giver of advice can explore together to their great mutual advantage. Only a confirmed bachelor-doctor, misogynist and pædophobe, has nothing to give or gain. The young father-doctor, in the thick of it with his own first-born, learning hourly and forced to advise, or the much older one who has forgotten some details but knows how to put them in their place, both these and many intermediates can, if they will, immensely help the young mother up against infant perversities and conflicting counsel. Erudition is not required. Common observation, common sense, a capacity for not being blown about by every wind of doctrine and a quite small fund of apposite knowledge will suffice. For example, the two words 'enough milk' comprise quite eight-tenths of the sacred mystery of baby feeding.

THE TODDLER

It is the same with the 'toddlers'. They composed and performed their 'variations on a nursery theme' long before Dohnanyi and they give innumerable performances year after year, yet never miss their intended effect. 'Not use my pot', 'not eat my dinner', 'not go to sleep' comprise the whole thematic material—it could even be shortened to 'not'; but so fertile are they in invention, so adept in the devices of augmentation, inversion and ornament that every mother believes her particular little fiend to be playing a new tune. The medical adviser can get quite a long way by assuring her,

with conviction, that the theme has the widest currency and that even the present variant has been heard before. It is more than time that this fruitful and delightful field of advisory practice was reoccupied. It should never have been allowed to pass, by default, into other hands.

SEX EDUCATION

I shall pass over the rest of childhood, though needs and opportunities for advising will not be lacking ('See that she gets the rubella. Yes, I'm serious. Don't miss a chance'.), and consider for a moment whether the medical adviser comes in at all on sex instruction and education.

I heard an experienced and respected woman psychiatrist say, not long ago, that there was a crying need for sex education but that she was sure the family doctor was not the one to give it. I would like to suggest that adequate sex instruction—if indeed it can ever be adequate—cannot come from a single source but that part of it can very well, perhaps even best, come from the family medical adviser. The biology of sex and reproduction, everything in it that we share with other living things, especially our fellow mammals, should be taught, carefully, progressively and thoroughly to every child in school, steps being taken to see that the parents know what is being taught. Schools should teach the facts—if they don't they will be taught and learnt in corners—and they should teach the facts dispassionately as if they were cold. But of course they are not cold. Stripped clean of all that clothes and grows from them—sexual passion, love, romance, all their sensual and spiritual attributes and evocations—the bare biological facts are, properly considered, among the most miraculous and wonder-inspiring in the whole realm of physiology, and that is saying something.

The headmistress of a day school for girls coming, for the most part, from what would be termed 'good class' homes, told me that her pubescent and adolescent girls knew the 'facts of life' as a matter of course but grossly, with contempt rather than respect, as though exchanging the dangerous innocence of Miranda for the no less dangerous but far less attractive knowledge of Caliban.

May not the family medical adviser be in a better position than anyone to convey to an adolescent boy or girl the conception of the body, and not least its reproductive mechanisms, as something to marvel at and respect and if he succeeds may not this wonder and respect stand the young man or woman in good stead when, in this age of vaporized values, they search for a basis for sexual morality?

Behaviour, except as it affects health, is not the doctor's province. The medical adviser can—I think he should—teach the plain facts of venereal disease and put masturbation in perspective. He should make the boy or girl know that they have in him an unshockable medical friend, with sympathy for them in the job of keeping their feet while Nature and civilization shove and tug in conflict (has he not tried it himself?), and that he is there to be consulted, questioned and confided in. More, I suggest, he would be rash to attempt. The extreme complexity and difficulty of the subject is what most impresses me and I am not reluctant to leave it.

YOUTH AND INTROSPECTION

Youth is the time when people should be, and often are, at their healthiest and when they should, and often do, have least need of a medical adviser but it is also the time when, notoriously, introspection buds and blooms and when doubts about the integrity of vital organs are sown or sow themselves and all too easily take root. Hearts and circulations, lungs and generative organs are the commonest objects of apprehension; brains and livers generally receive the confidence in their integrity they deserve and so, at this age, does the alimentary system (its turn comes later). Of course, there is commonly an iatrogenic factor, direct or indirect, and ironically enough the deadly seed may be sown by an examination, a 'keeping under observation' or a restriction of activity decreed in the name of preventive medicine or by some ill-conceived piece of 'health-talk', printed or broadcast. Sir James Mackenzie has some very relevant remarks:

> 'Many children are made to lead a restricted life', he writes, 'because the doctor discovers an abnormal sign—a murmur or an irregularity, or the child may have fainted. Children are very sensitive to *distress*. When the heart is exhausted distress is induced, and children instinctively cease their efforts on the first sign of distress, so that no harm is ever done by the child when left to itself. Even when the heart is damaged and its efficiency impaired, no harm will ever result if the amount of effort is left to the child's own judgment'.

Few of us, it may be, would agree without qualification but how often have I wished that at least the broad sense of Mackenzie's remarks had found general acceptance. What must be the sum of chronic cardiac invalidism such acceptance might have saved?

Here, in chronic invalidism, cardiac or other, is a common and most important field of action for the medical adviser, for it is rarely possible for anyone else to uproot the seedlings of this disorder and, if not uprooted young, they are commonly unuprootable. It may take two to do the job—a family doctor and a consultant, but for success they must work in the closest of close harmony. Even if it takes two it remains a personal task for which teams and institutions are wholly unfitted. Often enough, only the personal doctor has a chance.

CHRONIC INVALIDISM

And what chance has he? What is known about chronic invalidism—its origins, incidence, in terms of age, sex, social class, income, occupation and place of residence; of its natural history, relation to organic disease and response to treatment? Here, on the face of it, is yet another field for general practitioner research, important, for the condition must be extremely costly in man- or woman-work-days and in National Health Service expenditure (think of the x-ray bill alone!), but exceedingly difficult to institute. For the subject, though familiar to every experienced practitioner, is as elusive and polymorphic as Proteus himself and the ever-present fear of the cerebral tumour, the dark, secret carcinoma or the obscure manifestation of a collagen disease makes diagnosis, even confined within the doctor's own skull, perilous and forbidding.

Probably research is impracticable and yet the young doctor—perhaps most of all the intending consultant—should surely be taught that there is a disease, common among intelligent and amiable people, whose essence is inability to face the consequences of being quite well and whose sole constant manifestation is distrust of a vital organ. Doubtless the soil was prepared in the nursery or before but the seed is sown in a clinic or consulting room and I return to the question: can the medical adviser pluck the seedling out? In the nature of things one man's answer can rest only on personal experience, but whenever I have remarked to a fellow-practitioner that to attack even incipient chronic invalidism is the most thankless task in the whole of medical practice he has always cordially agreed.

Yet the rare success is very rewarding. To deflect a potentially useful fellow-citizen from the dismal round of investigation, reinvestigation and constant or recurrent therapeusis, to convince a young doubter that his heart, for example, is as strong and unstrainable as a heart can be gives as full and lasting satisfaction as does the saving of a life physically endangered. Directly or vicariously Sir James Mackenzie must have rendered this service to many young people by his disentangling the insignificant from the significant irregularities of the heart-beat, but it is a service which cannot be rendered or received by a group. An impersonal voice addressing all those who believe they have second-rate hearts will, quite obviously, persuade no one of them to embrace a stronger faith. Someone must stand proxy to Mackenzie and who can it be but the personal medical adviser?

If it be said 'but this is psychiatry and in a properly organized medical service would fall to the psychiatrist', the answer is that if a young man thinks his heart is at fault the last kind of specialist he will see is a psychiatrist—a heart-surgeon would be more to his taste—and even if he would there are never likely to be enough psychiatrists to go round.

In passing may I suggest that to label the chronic invalid 'neurotic' or even to call his concern over his heart, bowel, back or blood pressure a neurosis is to do him an ill service. If the word gets about—and words have wings—it will convince all his friends that we consider he is shamming and will faintly suggest to us that here is a disease—a neurosis—requiring exorcism or other treatment rather than a disabled person requiring advice, persuasion, guidance and reiterated reassurance.

Except perhaps for infancy, there is no close season for invalidism. I have chosen youth as the time to discuss it only because youth once past, the chances of prevention or cure are very small indeed.

THE MENOPAUSE

With youth we are nearly round the life-cycle but of course the life-cycle is only part of life. Having reproduced, off we go on a tangent towards eternity and the first milestone is middle age. I once read an advice-book on middle age which implied that for most it was a dreary *hinterland* between 'those blue remembered hills' of youth and the swamps or rocks of age. I

have not found it so and I hope I am not exceptional but, flat or not, it contains for the medical adviser one unique and notable feature—the menopause. The menopause casts its shadow before it and if our adviser has by now earned the trust that should be his he will be asked about it long before it comes.

A male adviser, immune from direct experience, must needs speak with diffidence but may feel able to say that neither suicidal nor murderous impulses nor even mistaking red traffic lights for green, are necessary ingredients and that it is quite common to emerge recognizably still oneself. If he does feel thus able, what he says is often well received and may come more comfortingly from him than from the little books or from 'this column' —even if it is to be found there—but is he justified? Frankly, I do not know and I suggest that here, in the symptomatology of the uncomplicated menopause is a worthy subject for general practitioner research. The manifestations, subjective and objective, of 'ceasing to be after the manner of women' would be the sole matter for inquiry; causes and cures would be outside the terms of reference. One medical adviser at least would have felt in a far stronger position if he had known all the answers.

Although males escape the menopause they have their climacteric and are by no means immune from introspective anxiety requiring medical advice in middle or any other age. Indeed, we should probably all agree that the bred-in-the-bone worrier is more often male than female.

THE ELDERLY

If, as John Morley said, 'the great business of life is to be, to do, to do without and to depart' the medical adviser can help considerably in the last two undertakings. This is an age of 'iatricians' and I suppose there is room for the 'ger-' as for the 'pæd-' but, in my opinion, a good medical adviser should not leave much for them to do—at least in the field of advice. It does help old people to know that many minor losses—loss of automatic balance, of high-tone hearing, of undazzled vision against the light, of memory for names and things just done, of ability to keep warm and keep awake, of agility and physical endurance—are common to most of us in age and must, within reason, be accepted, though they can often be dodged or compensated.

The medical adviser will be asked to solve conflicts:—

> 'My daughter says I mustn't sleep alone in the flat, but I'm not afraid of dying, I have a telephone and I would *loathe* a companion'; or, from the other side, 'Doctor, will you please tell father he is not to mow the lawn!'

Here, again, I am sure the practitioner should stick to advice and refuse to give orders but he can scarcely refuse help in these conflicts between 'safety first' and cherished independence, and he may find solutions.

Lastly, departing. Here practical help in smoothing the path rather than words is likely to be demanded of the practitioner but there is still a place for advice. 'To tell or not to tell' will turn up time and again and I wish only to say that I am sure the words 'always' and 'never' are equally out of place. I

am sure the *ideal* is for everyone concerned to be courageously 'in the know' together, facing death open-eyed, and I am sure that, though this ideal is often unattainable, it should not on that account be discarded.

THE DOCTOR AS INTERPRETER

I have given a sketchy sketch of the medical adviser and his functions on my chosen basis of ages but, because it belongs to no one age, have said nothing of him in the vital role of interpreter.

The old are, on the whole, incurious and babies cannot ask but most others, of every intermediate age and every social, cultural and economic class, want to know, to understand what is wrong, what is to be done and why, whether they can help and how. I have already mentioned some who do *not* want to know. For myself I not only welcome them but greatly respect them. I suspect they have the best prognosis, but they are a minority. Most want to understand and can be good patients only if they do understand. Emphatically they include intelligent children—and many children are highly intelligent. They include the East End mother who complains that at the other hospital where she took him she 'didn't get no satisfaction'. She is not complaining of negligence in investigation or treatment; she means that they failed to explain. It is becoming common form for lecturing or paper-reading practitioners to report once more the reiterated complaint of the patient returning to the fold: 'Of course they don't tell you anything and there was no-one I could ask', and in the many written patient-sagas now appearing the phrase 'if only someone had told me' almost always appears at least once.

Hospitals are busy places, staffed by teams in which responsibility is deputed or shared; if the chief talks to one patient he must talk to all and both time and privacy are hard to come by. 'Reasons are plenty as blackberries' but the hard fact remains that time and again the patient returns from the hospital—and for that matter from the private consulting room—with questions unanswered or unasked and dark speeches unilluminated or misapprehended. Once again there is only one possible source of light: the personal medical adviser.

'A GOOD THING'

I hope I may have convinced any who needed convincing that there is a field of medicine which is the personal adviser's own, in which only he can effectively work and that he and the work he does together constitute 'a good thing' and should therefore continue to exist. But will they? Can they? A quiet unintended liquidation seems such a likely fate.

Suppose him gone and his works with him, the mortality rate would be quite, and the morbidity almost, unaffected. Those accustomed to consult him or brought up to count on him would, for a time, 'feel quite lost' but this would pass, there would be no public outcry for his re-establishment and the Ministry would not notice the difference. The fragmentation of medicine,

the adulation of teamwork, the curious belief that uniformity is somehow identical with justice, the unquestionable fact that he is, as they say 'uneconomic'—all these militate against him. His chances seem poor and yet if he goes the sum of human unhappiness, great enough already, will be greater and the satisfaction of medical practice to the practitioner will be less.

I had written thus much when news came that in the view of a professor of social medicine my unheroic hero, or someone very like him, was already dead. 'One might almost say', said my friend, Professor Backett, 'that the "guide, philosopher and friend" part of his job is out—finished'. He shed no tears over this but added that 'at worst it was a pompous and essentially curative idea anyhow'. He did not say what sort of an idea it was at its best. Now it would ill become a James Mackenzie lecturer to attack Professor Backett's main theme—that the future task of the family doctor is presymptomatic diagnosis and the strangling at birth of diseases at present unrecognized even in their infancy, for this is but an extension of Mackenzie's reiterated plea for diagnosis before the appearance of signs. I cannot, however, let pass the statement that the medical adviser—if this is indeed he—is already 'out, finished'. True, doctors are not philosophers—a strange race who dispute in a secret language—and an adviser is not precisely a guide but we need not quibble; it is for him that the professorial bell tolls. Is he indeed dead? Knowing something of many members of this College, I cannot believe it. Is he 'finished', in the sense that his job is done? I strenuously deny it and have given reasons. Is he in peril? Assuredly; but if enough practising medical advisers and if, in particular, our College is determined that he shall live and not, in the name of preventive medicine, be replaced by an iatrocrat, then I believe he need not die.

AN INDISPENSABLE REQUIREMENT

And if, as I hope, we turn up our imperial thumbs what must we do to save him alive? Two things. First and foremost, keep his ξιδωλον—*imago*, picture, image—shining, steady and bright, before the eyes of all concerned—teachers and taught, young adventurers in medicine, established practitioners, 'ever climbing up the climbing wave' and perhaps getting tired of it, even our far too patient patients, all too ready to take what comes. And second, not to cease from mental or even from less rarified forms of fight, nor let our sword sleep in our hand until we secure for him his one indispensable requirement—*time;* time to listen, to think and to talk. If we succeed and he and his works continue, then those who preserved his life will deserve well of medicine and will have done something to redeem the time.

GENERAL PRACTITIONER CLINICAL TRIALS

NIALAMIDE ('NIAMID') AS AN ANALGESIC AND IN ANGINA PECTORIS AND ASTHMA

NIALAMIDE ('niamid') has an established use as a monoamine-oxidase inhibitor, in the treatment of depressive illness. In addition, there have been reports suggesting that this drug may also have analgesic properties, both by itself and as an enhancer of narcotics. Amine-oxidase inhibitors have also been used to relieve the symptoms of angina pectoris, and since amine-oxidase antagonism results in a rise in catechol amines (i.e. adrenaline and noradrenaline) in the tissues, it occurred to us that it might also have some effect in the treatment of asthma.

SCOPE OF INVESTIGATION

General practice offers a wealth of chronic painful conditions, such as the various forms of arthritis and non-articular rheumatism, in which there is often a real need for some analgesic midway in action between the aspirin group and the morphia group, but without habit-forming properties. This trial was undertaken to try and elucidate some of these points, and the dosage was standardized at 2 tablets (x 25 mg.) twice or thrice daily, and the participants were instructed to reduce this dose to the minimum effective level for maintenance purposes. Only patients with symptoms of at least three weeks' duration were included in the trial.

A total of 61 patients was studied in the trial, consisting of 50 patients with prolonged pain, three patients with asthma, and eight patients with angina pectoris. The commonest types of condition causing chronic pain were non-articular rheumatism, osteoarthritis and rheumatoid arthritis, in that order. Of the previous drugs used in these conditions, the aspirin group had produced completely satisfactory analgesia in 26 per cent. of the patients, and a partial analgesia in a further 55 per cent. It is apparent therefore that with these previous drugs there was a large group of patients in whom analgesia was not completely effective. Where narcotics had been used, the percentage of complete relief of pain rose to 85 per cent. with a further 15 per cent. of patients obtaining partial relief of pain. These results tend to underline the need already mentioned for an effective analgesic midway in action between the aspirin and narcotic groups. All the angina patients reported obtaining complete relief of pain temporarily with the use of glyceryl trinitrate tablets, but with long-acting coronary vasodilator drugs the results were very disappointing, as no patient in this trial reported any relief of pain with these preparations.

RESULTS

The effect of nialamide in relieving pain was judged as follows: + = completely effective ; ± = partially effective; — = no effect. The results at intervals of one, three and five weeks are shown in table I. This shows rather similar results for the different conditions treated, with a slight trend

Condition	1st week			3rd week			5th week		
	+	±	—	+	±	—	+	±	—
Osteoarthritis	1	1	9	2	3	4	2	4	2
Rheumatoid arthritis	1	2	5	1	1	6	1	–	1
Non-articular rheumatism	1	8	4	3	4	3	1	2	–
Post-herpetic neuralgia	Side-effects necessitated early omission								
Multiple sclerosis	–	1	–	–	1	–	–	–	–
Diabetic neuritis	–	–	1	–	–	1	–	–	1
Gastro-intestinal pain	2	1	1	–	3	1	1	1	1
Intermittent claudication	–	–	1	–	–	1	–	–	1
Cancer	3	4	1	1	3	2	1	3	1
Cancer + Narcotics	–	1	1	1	–	–	1	–	–
All (nialamide alone)	8	17	22	7	15	18	6	10	7

TABLE I.—Results obtained with nialamide as an analgesic.

to improvement in the fifth week. Nevertheless, even in this, the best week, only 26 per cent. of patients obtained complete relief of pain with a further 43 per cent. obtaining partial relief. Since these figures are not as good as those obtained with the aspirin group, it was concluded that nialamide has little use in this type of patient in general practice. Only two cancer patients were given nialamide, in addition to their usual narcotics, and no significance can be attached to the results obtained, but in neither case was it possible to reduce the dose of narcotics given.

The results obtained in angina pectoris and asthma are shown in table II. It is seen that several patients with angina pectoris did seem to improve on nialamide, particularly in the fifth week. This improvement was evi-

Condition	1st week			3rd week			5th week		
	+	±	—	+	±	—	+	±	—
Angina pectoris	–	3	5	–	5	2	2	1	2
Asthma	–	1	2	–	1	1	–	1	–

TABLE II.—Results obtained with nialamide in eight patients with angina pectoris and three with asthma.

denced by a reduction in the number of attacks and the number of trinitrin tablets required, and also by the improvement in effort tolerance. In view of the poor results obtained in the pain trial, it would seem that this improvement must be due to some actual effect on the cardiac condition.

Two of these patients developed coronary thrombosis while under treatment and, although this may have been entirely due to chance, there is the possibility that this could have been caused by a hypotensive effect of the drug. It was felt that a larger series of cases should be studied, before nialamide could be recommended for the treatment of angina pectoris in general practice.

SIDE-EFFECTS

The majority of patients (69 per cent.) experienced no side-effects at all with nialamide, but 7 per cent. had to omit taking it because of side-effects. No particular side-effect was very prominent, although vertigo (10 per cent.) was the commonest, the others reflecting the usual 'mixed bag' of side-effects encountered with almost any drug tried.

CONCLUSION

We were not impressed with nialamide as an analgesic by itself, although we did not have sufficient opportunity to evaluate this drug as a potentiator of narcotics. In the treatment of angina pectoris, there did seem to be some definite improvement in the degree and rate of attacks, and we await with interest work done on a larger series of cases. In asthma, we did not see sufficient cases to make any evaluation of the drug.

The following doctors took part in this investigation:—
Dr. Derek Clarke, Streatham, London, S.W.16.
Dr. J. D. S. Knight, Hoddesdon, Herts.
Dr. D. C. Morrell, Hoddesdon, Herts.
Dr. J. Saperia, Leyton, London, E.10.
Dr. F. V. Simpson, Scarborough, Yorkshire.
Dr. David Wheatley, Twickenham, Middlesex.

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DEMETHYLCHLORTETRACYCLINE ('LEDERMYCIN') IN CHILDHOOD INFECTIONS

It is claimed that demethylchlortetracycline ('ledermycin') results in higher and more prolonged blood levels of chlortetracycline than equivalent preparations of the parent antibiotic itself. Since there is no pædiatric preparation of chlortetracycline available in this country, it was decided to compare demethylchlortetracycline pædiatric drops with tetracycline pædiatric drops. The differences between the various tetracyclines, at least in the treatment of the infections studied in this trial, are so slight that for all intents and purposes this is equivalent to comparing demethylchlortetracycline with the parent substance.

SCOPE OF INVESTIGATION

Demethylchlortetracycline was administered in a dose of 3 mg. per pound (6.5 mg. per kg.) body weight daily, divided into two daily doses, and tetracycline was administered in a dose of 6 mg. per pound (13 mg. per kg.) body weight daily, divided into three daily doses. Thus, a one-year-old child received 10 minims (0.6 ml.) of demethylchlortetracycline drops twice daily or alternatively 8 minims (0.5 ml.) of tetracycline drops thrice daily, and in proportion for other ages. A total of 79 children were treated with the two preparations, of whom 39 were treated with tetracycline and 40 with demethylchlortetracycline. These cases were seen in five different practices, in different parts of the country. Children up to 7 years of age were treated, and the age-groups were on the whole similar between the tetracycline-treated series and the demethylchlortetracycline-treated series. Only cases of acute infection within forty-eight hours of onset were treated, and the commonest infections treated were tonsillitis, otitis media and bronchitis, of which equal numbers were treated with the two preparations. Other conditions treated were pneumonia, styes, cystitis, dysentery and dental abscess.

RESULTS

The results were uniformly good with both preparations, in all the conditions treated, and the results were similar from the different practices. These total results are shown in table I.

Result	Tetracycline	Demethylchlortetracycline
+	30	36
±	7	3
—	2	1
Days to clear		
1-3	23	29
4-5	10	9
6-10	4	1
Failed to clear	2	1

TABLE I.—Results obtained with tetracycline and demethylchlortetracycline in acute infections in children.

The results are shown as:—
+ = complete and rapid resolution.
± = slow resolution or recurrence on omitting treatment.
— = no effect.

There was a slightly better cure rate with demethylchlortetracycline, in that 90 per cent. of the cases on this antibiotic cleared up rapidly, with a complete failure rate of only 2.5 per cent. This compares with a 77 per cent. complete cure rate and a 5 per cent. failure rate with tetracycline. It is doubtful whether these figures have much significance from the practical

point of view, since virtually the same number of cases can be cured with tetracycline as with demethylchlortetracycline. The figures for the time taken to resolve also show slight superiority for demethylchlortetracycline.

All but 5 per cent. of the patients taking the tetracycline drops liked the preparation, whilst all the children taking the demethylchlortetracycline drops liked it with the exception of 7 per cent. Both preparations therefore appear to be eminently suitable for giving to children in general practice.

SIDE-EFFECTS

Side-effects were very few indeed and 98 per cent. of the children taking tetracycline and 92 per cent. of those taking demethylchlortetracycline experienced no side-effects at all. Vomiting occurred in one patient on tetracycline and in two patients on demethylchlortetracycline, and a slight sore tongue developed in one other patient on demethylchlortetracycline.

CONCLUSIONS

It is concluded from this trial that both preparations are highly effective in the treatment of these common infections in young children and that there was really little to choose between the two preparations although the figures did show a slight superiority for demethylchlortetracycline. The twice-daily dosage schedule employed with demethylchlortetracycline proved to be entirely satisfactory, and this is a very practical dosage scheme to use in general practice. From the point of view of patient acceptability and side-effects, both preparations were well tolerated. It must be remembered, however, that the conditions treated in this trial are often not treated with a broad-spectrum antibiotic, but rather with oral penicillin in the first instance. This trial was designed merely to test the effectiveness of the two tetracycline preparations, and we would not advocate that such preparations should be used in the first instance in the treatment of these conditions. The choice of treatment in these common childhood infections is, of course, at the discretion of the individual doctor.

The following doctors took part in this investigation:—
Dr. J. H. Davidson, Dulwich Village, London, S.E.21.
Dr. T. P. McB. Kelly, Coleraine, N. Ireland.
Dr. D. C. Saunders, Rhondda, Wales.
Dr. J. M. Stewart, Portsmouth, Hants.
Dr. David Wheatley, Twickenham, Middlesex.

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SECTION OF GENERAL PRACTICE OF

THE ROYAL SOCIETY OF MEDICINE

DISCUSSION ON INFECTIOUS DISEASES TODAY

November 16, 1960

Dr. G. I. Watson (*Peaslake, Surrey*).—Infectious diseases today fall into three groups: (1) Those in which the family doctor can make a final diagnosis unaided, (2) those in which the complete diagnosis rests on microscopic or serological findings, and (3) those with which the laboratory cannot help at present.

OBSERVATIONS OF A COUNTRY G.P.

The following are the observations of a country general practitioner on the various diseases.

Measles.—Notification serves no useful purpose. Vaccination should be pressed for. Measles in infants is now normally milder than in schoolchildren; breast-feeding significantly contributes to this mildness, whether or not the mother has had measles.

Influenza.—A study of fever charts and other evidence suggests that the characteristic biphasic fever pattern occurs when a patient is reinfected with virus from himself before becoming immune. A study of serial intervals suggests that convalescent carriers are an important means of spreading influenza.

Rubella.—Infection of a mother about the time of conception seems particularly likely to cause severe fœtal damage. I have often wondered whether there are two sorts of rubella, only one causing fœtal damage.

Glandular fever.—Toxoplasmosis may cause fœtal damage and is a possible alternative diagnosis, when the Paul Bunnell test is negative.

Streptococcus pyogenes.—Of 182 patients with fever and sore throat in one year, 71 had a bacteriologically positive swab, 55 were due to viral infections, and 62 others had negative swabs or were not tested. Of the 71 positive throat swabs, 65 yielded group A streptococci and 15 were of type 12; the next commonest types were 1, 6 and 3. December (18), November (15) and January (11) were the peak months; no isolations were made in June, July or August. Children were more often affected than adults, especially before the New Year. Acute nephritis was associated with type 12,

and scarlet fever with types 3 and 3/13. No rheumatic fever was seen during the same year.

Catarrh.—The incidence varies with age and reaches a peak earlier in towns than in the country, suggesting an infective basis.

P.U.O.—Of 120 patients with non-bacterial febrile illnesses in one year, laboratory confirmation of the diagnosis was made in 32 (25 per cent.). New names are needed for some of these diseases.

'*Shere fever*'.—A few cases of this infection, which is due to Coxsackie A virus, appear most years during July, August and September and resemble non-paralytic poliomyelitis.

P.U.O. with rash.—This occurs mainly in the same months as 'Shere fever'. Roseola infantum may be due to Coxsackie or ECHO viruses.

Poliomyelitis.—I have records of a family outbreak of non-paralytic poliomyelitis in which one or both primary cases (children) remained infectious for 18 to 25 days before infecting their father. Immunized children can become healthy or convalescent carriers. I have been impressed by the evidence of Dane and Donaldson, from Belfast, of the danger of using drugs which allow a patient to increase his activity by suppressing the symptoms of pre-paralytic poliovirus fever.

Adenovirus infection.—During a twelve months' period, 44 cases were diagnosed (21 confirmed), the majority being type 3 in which nasal obstruction was marked. The characteristic fever did not usually reach its peak in the first twenty-four hours and I found that pyrexia over 100° F. (37.8° C.) might last two to six days, without the children feeling very ill. Convalescence was rapid.

Coxsackie type B virus.—This, too, is a common infection, causing 'febrile headache', Bornholm disease, afebrile thoraco-abdominal pain, or sudden transient pyrexia in an infant.

WP/60 (biphasic febrile pneumonitis).—This is the code number and name, which have been given to a condition which I first encountered as an influenza-like epidemic among young children in January 1960. Bacteriological and virological investigations were uniformly negative and cold agglutinins were not demonstrable in the blood. Investigations by the epidemic observation unit of the College of General Practitioners produced reports of 430 cases scattered throughout Eastern England, London and the Home Counties and Scotland (Annual Report of College of General Practitioners, 1960).

Atypical primary virus pneumonia.—Three family outbreaks occurred in my practice this summer. The disease was highly infectious, involving 16

out of 19 people from June to October at serial intervals of two weeks or more.

Reference

Annual Report of College of General Practitioners (1960): *The Practitioner*, December 1960, Supplement p. 25.

Professor C. H. Stuart-Harris (*University of Sheffield*). Technical advances have enormously expanded the virologist's ability to recover and study viruses related to human diseases. On the other hand, mere recovery of virus from secretions, tissues or excretions does not by itself constitute proof of causal relationship. Indeed, one of the most important problems today is the task of investigating further the exact relationship between viruses and disease. Criteria similar to Koch's postulates must be applied, particularly that of reproduction of disease by inoculation of cultures.

Much of our present knowledge stems from the revival of tissue culture methods by Enders and the recognition by Tyrrell and Parsons of cytopathic changes in cultures of cold virus, at 33° C. In view of the multiplicity of viruses, especially from the alimentary and respiratory tracts, serological methods of identification have proved a bugbear. In working with newly recognized viruses, it may therefore be easier to recover virus from throat-swabs or stools in tissue-culture.

RELATIONSHIP BETWEEN SYNDROMES AND VIRUSES

Smallpox.—The laboratory helps greatly here with culture of virus from crusts, and serological confirmation using antigen from crusts.

Measles.—Attenuated virus immunization is still experimental, and shows clinical reactions similar to measles modified by gamma globulin. The interrelationship between measles and dog distemper virus, although not yet proven, is perhaps similar to that between lymphogranuloma and psittacosis, and between influenza A and fowl plague, and is possibly significant in relation to the evolution of viruses.

'*Roseolum infantum*', first recognized by Neva in Boston, is due to enteroviruses: chiefly ECHO type 9 in Great Britain. These viruses are also associated with aseptic meningitis. These changing manifestations of attack represent an altered pattern of host-virus interaction due to less subclinical infection in infancy, which in turn is due to better care and hygiene. We may expect further changes in the patterns of attack. It is also recognized that one syndrome, 'aseptic meningitis', may be due to many different viruses, including all 28 ECHO viruses.

Acute respiratory syndromes.—There are many ill-defined such syndromes, and the number of known viruses is increasing every year. Influenza viruses show constant antigenic change, whereby their recurrent attack is maintained. Fortunately, variation has not recently been in the direction of increased virulence, but we do not know whether there is still an infinite further number of variations. Atypical pneumonia, common during the

1939-45 War, has persisted in localized outbreaks in Service establishments in the United States: the virus is being further studied by the new technique of fluorescent microscopy.

The major advance in the study of the various 'cold' producing agents is their culture at 33° C., and the finding that these viruses are unable to produce their cytopathic effects when grown at 37° C. The febrile catarrhs, due to viruses showing many serological types, exhibit local outbreaks in infants, children, and in military establishments. Other types studied include para-influenza, croup-associated, hæmadsorption, COE and REO viruses. The picture of the acute respiratory viruses is of a jungle of microbiology, set alongside the many poorly defined acute syndromes of the human respiratory tract.

Dr. S. Leff (*Medical Officer of Health, Willesden*).—Although many common infectious diseases are more benign than in the past, and diseases such as cholera and typhus have been eclipsed and others such as smallpox and diphtheria are on the wane, much disability, and work for the general practitioner, are still caused by these conditions.

SOME COMMON INFECTIOUS DISEASES

Measles.—In the epidemic years—usually every other year—there are up to 600,000 cases with about 100 deaths, almost as many as occur from poliomyelitis. Although the condition is much more benign than it used to be, secondary infection with streptococci, particularly in young children, can result in serious disease. A more serious complication is encephalitis. In a recent investigation more than half the patients showed abnormal electroencephalograms, the abnormality persisting for months and even years in about 1 per cent. of these. Gamma globulin can be used to prevent or attenuate an attack in day nurseries, but this substance is expensive and in short supply. A vaccine has been used in Panama but, although protection seemed to result, it produced fever and rashes in many of the subjects.

The mortality-rate for *whooping-cough* is about four times that of measles, and the disease is very difficult to diagnose. More accurate diagnosis would lead to better clinical assessment of drugs which might shorten the disease. Hyper-immune gamma globulin has proved ineffective and we must rely on early diagnosis, isolation and antibiotics to control secondary infection.

Scarlet fever is now relatively mild, with a death rate only half that of measles. Type 12 strain of Griffith streptococci often causes acute nephritis and penicillin may be given prophylactically to those in close contact with such cases.

There has been a spectacular reduction in the number of *diphtheria* cases and deaths, but the disease is still with us. In 1957 there were only 27 cases with 4 deaths, but in 1958 this rose to 80 cases with 8 deaths, whilst in 1959 there were 102 cases but no deaths. Diphtheria immunization has fallen, and the proportion immunized is now less than 50 per cent., prob-

ably because of the time absorbed in dealing with poliomyelitis vaccination.

The answer to *poliomyelitis* would now appear to lie in vaccination since in 1959 there were only 2.3 cases per 100,000, and this year it may be even less. In the past, men have been more affected than women, although 5 per cent. more women were paralysed. The highest proportion of paralysis cases occur in infancy, from 0 to 4 years, although there has been a 70 per cent. reduction in mortality in this age-group. The smallest fall in the death rate was 25 per cent. in the 25 years and over age-group. Many cases diagnosed as non-paralytic poliomyelitis have turned out to be cases of aseptic meningitis, caused by such viruses as mumps, lymphocytic choriomeningitis, herpes simplex, Coxsackie, ECHO viruses.

It has been estimated that 30 per cent. of general practice is concerned with *virus respiratory diseases*, resulting in an enormous economic cost. 'Influenza' covers many acute febrile respiratory diseases, which may have a varying etiology. Severe bronchiolitis in infants may be caused by adenoviruses, which may also cause pharyngitis, conjunctivitis, acute febrile diseases, tracheobronchitis and atypical pneumonia. These viruses may also spread through the gastro-intestinal tract, and cause outbreaks in institutions.

Dysentery has become more widespread than formerly. In the peak year, 1956, the number of cases reached almost 50,000, but the number of deaths has been relatively small. This is doubtless due to the notification of symptomless carriers. The main method of spread has been through lavatory seats, and improvement in hygiene is needed, particularly in schools. Control of this disease consists of early detection and treatment of patients, cleaning and disinfection of lavatories, and improvements in washing facilities in institutions.

FOOD POISONING

Food poisoning remains a major public health problem, and there are probably at least 50,000 cases per annum of Salmonella poisoning in this country. The proper investigation and control of these cases require detailed epidemiological studies in every case, whether sporadic or epidemic. Salmonella is widespread among many foodstuffs, and staphylococcal infection is also common. The latter is spread from skin lesions, semi-preserved cold foods being often contaminated by hand. The preservative salts are ineffective against staphylococci and milk can also be easily contaminated. *Clostridium welchii* also commonly causes food poisoning, the only effective method of control lying in regulating the cooking and storage of meat dishes.

CURRENT THERAPEUTICS

CLVII.—THE PRESENT STATUS OF THE SULPHONAMIDES

By T. H. CROZIER, M.D., F.R.C.P., D.P.H.

Physician-in-ordinary to H.E. The Governor of Northern Ireland; Physician, Royal Victoria and City Hospitals, Belfast

THE time is opportune to review the position of the sulphonamides in contemporary therapeutics.

HISTORY

Certain azo dye compounds synthesized during the first decade of the present century were known to exert an antibacterial effect; many were clearly active *in vitro* but not *in vivo*. Gerhard Domagk became interested in the problem, and identified the bacteriostatic property as a function of sulphonamide groupings in the azo compounds. In 1935 he published full laboratory and clinical evidence of the efficiency of sulphonamides in coccal infections. This chemotherapeutic triumph was most dramatically followed up by Colebrook and Kenny (1936) who showed excellent results in puerperal fever and septic abortion—conditions previously almost uniformly fatal. Many other diseases due to coccal infections (meningitis, pneumonia, erysipelas) cleared as if by magic under the influence of sulphonamides.

Modification of the chemical structure of sulphanilamide was found to accentuate activity against certain groups of bacteria. Sulphapyridine, introduced in 1937, proved superior against pneumococcal infections and more efficient generally than sulphanilamide, albeit more toxic. Sulphathiazole (1940) was thought less potentially hazardous than sulphapyridine and the most effectual in staphylococcal diseases. The war years saw the introduction of the less toxic and more acceptable pyrimidine compounds —sulphadiazine, sulphamerazine and sulphadimidine—and these remain the backbone of sulphonamide therapy today.

In the search for rapidly absorbed oral sulphonamides, some were found to have parodoxically slow absorption, exerting their bacteriostatic action mainly on the intestinal contents. This fortunate accident led to the first effective therapy of dysenteric diseases.

The alarm and despondency engendered in the medical staff of the Middle East Forces by information that a transport containing the country's main stock of sulphaguanidine had come to grief through enemy action may be imagined! Confidence, however, returned to the military physicians' breasts on the discovery that the current soluble and absorbable sulphonamides were also effective in bacillary dysentery.

Sulphaguanidine was in time replaced by phthalylsulphathiazole and succinylsulphathiazole, with absorption figures of only 5 per cent. which slowly liberated sulphathiazole during passage down the gut.

The principle of sulphonamide-combination marked a notable advance.

One of the early bugbears was the comparative insolubility of the sulphonamides and their acetyl products. Crystalluria, with mechanical tubular blockage and nephrotoxicity, sometimes proved fatal. Adequate solubility was therefore an essential attribute, and some otherwise admirable compounds failed in this way. It was shown by Lehr (1957) that poor solubility was a much more important factor in renal damage than chemical toxicity. Adequate fluid turnover and alkalinization of the urine are essential during any form of sulphonamide medication. Lehr demonstrated that mixtures of partial dosages of several sulphonamides show substantially less tendency towards development of renal tubular obstruction by crystals than any single compound of the mixture in total proportionate dosage. Trisulphonamide tablets B.P.C., containing sulphadiazine, sulphathiazole and sulphamerazine, is a popular and excellent preparation for general use, as well as for coliform urinary infections.

The search for more satisfactory sulphonamide compounds continues, and has of late given rise to several rapidly absorbed, slowly excreted preparations: sulphamethoxypyridazine has proved very satisfactory over several years of clinical trial. Still later developments in the same field are sulphaphenazole and sulphadimethoxine. After a single dose, traces of these drugs are detectable in the blood for several days, and the half-life of sulphamethoxypyridazine is placed at sixty hours by Jones and Finland (1957). Combinations of these with the older compounds are now available, but it is too soon to assess their value. It has been claimed also that these long-acting compounds show enhanced activity against certain bacterial groups, but again further evidence is awaited on this point.

MODE OF ACTION

The rapid disinfectant action of sulphonamide in the blood stream is not understood. Although laboratory evidence is conflicting, it seems that with conventional dosage schedules the action is bacteriostatic rather than bactericidal. The essential link is *para*-aminobenzoic acid, a requisite for micro-organismal growth, and sulphonamides appear to compete with them for it. Direct chemical antisepsis counts for little, and sulphonamides induce neither increased immunological response nor heightened phagocytic activity. With few exceptions the sulphonamide antibacterial spectrum is uniform for the whole group of compounds; cross-sensitivity and cross-resistance on the part of individual organismal strains do not occur so that, in practice, selection of a sulphonamide for a given case is usually dictated by considerations other than the identity of the infecting organism.

Resistance to sulphonamide may be induced in all normally sulphonamide-sensitive micro-organisms, but particularly *N. gonorrhœæ*. In practice, prolonged ineffective treatment is most likely to induce insensitivity.

SULPHONAMIDE-ANTIBIOTIC COMBINATIONS

Weinstein and his associates (1957) have shown that the emergence of

resistance of some bacteria to antibiotics can be suppressed by the addition of sulphonamides; for example, they found streptomycin plus sulphadiazine or sulphafurazole better against *H. influenzæ* meningitis than the antibiotic alone. The micro-organism should initially be sensitive to both agents. Other endemic strains of this organism have been found to respond excellently to a sulphonamide-chloramphenicol routine. Bigger (1950) adduced evidence of a synergistic effect from sulphonamide-penicillin combinations, but as a rule combinations with bacteriostatic antibiotics, particularly the tetracyclines, are unhelpful. There is no evidence in favour of sulphonamide-antiserum combinations; indeed the advent of sulphonamides sounded the passing-bell of pneumococcal, streptococcal and meningococcal antisera. Many other examples of the utility of sulphonamide-antibiotic combinations may be cited from current therapeutics. Penicillin-sulphonamide treatment is routine in some countries for gonococcal infections, as well as pneumococcal infections, particularly meningitis. Many combinations of penicillin and sulphonamide are available commercially, and, whatever the wisdom of mixing two potent drugs in one tablet, they are effective in practice and enjoy considerable favour among general practitioners. Actinomycosis, anthrax, brucellosis, *E. coli* septicæmias (particularly meningitis) often respond well to a sulphadiazine-streptomycin routine. The first three of these infections, however, often run a tedious and unresponsive course, and repeated sensitivity tests should govern therapy; many permutations of the sulphonamide-antibiotic group may be necessary to achieve cure. Acute epididymitis (usually coliform) is best treated with trisulphonamide tablets, 2 g. followed by 1 g. four-hourly for five days, with or without streptomycin according to sensitivity.

INDICATIONS

There is a large and important group of diseases in which, unless the infection is fulminant, the patient debilitated, or special sensitivity tests indicate use of antibiotics, sulphonamides would serve equally well. Pneumonia, acute bronchitis, erysipelas, influenza, chancroid and acute urinary infections are mostly sulphonamide-sensitive. Some diseases are preferably treated by sulphonamides alone: e.g. coliform urinary infections and prophylaxis thereof during catheter life, dermatitis herpetiformis, erysipeloid and pyogenic granulomas, lymphogranuloma venereum and *Nocardia* infections. With regard to acute urinary infections, Carroll (1957) found that the soluble sulphonamide preparations are preferable when the infecting organism has not been identified. Many cases of pyelitis due to coliform infection respond quickly to moderate dosage with moderate fluid intake: e.g. sulphafurazole, 2 g. followed by 0.5 g. four times daily, and a fluid intake of 3 pints (1.75 litres).

Organisms sensitive to sulphonamides.—Hæmolytic streptococci and staphylococci (some strains); pneumococci; *E. coli* (most strains);

N. gonorrhœæ and *N. meningitides; H. pertussis, H. influenzæ* (some strains), and *H. ducreyi; Sh. dysenteriæ;* the virus of lymphogranuloma venereum.

CHOICE OF SULPHONAMIDE

From an embarrassingly wide range of general-purpose compounds, a few representative preparations may be mentioned as being of proven efficacy and safety:

Sulphadiazine B.P. diffuses rapidly, giving a high concentration in the blood and tissue fluids (particularly the cerebrospinal fluid). It is useful in treatment of meningococcal meningitis. As it is sparingly soluble in the urine, crystulluria occasionally complicates therapy.

Sulphadimidine B.P. is characterized by rapid absorption, diffusion and excretion. Satisfactory blood concentrations are obtained with six-hourly dosage. Possessed of good solubility, even in acid urine, it is one of the most reliable and safe compounds.

Sulphamerazine B.P. is rapidly absorbed and slowly excreted, giving high and sustained blood concentrations. This means that lower or less frequent dosage is permissible, and intravenous loading is rarely necessary. On the other hand, it is slightly more toxic than sulphadiazine and sulphadimidine.

Trisulphonamide tablets B.P.C. give an excellent clinical response with freedom from renal upset. They are widely used for urinary infections, but there is no reason why use of this preparation should be so limited.

Sulphafurazole B.P.C. has similar properties to sulphadimidine, and is equally popular.

DOSAGE

Routine oral medication for adults, using one or other of the compounds mentioned above, is:—

> Oral loading dose of 4 to 6 g., followed by 1 to 2 g. at four-hourly intervals (sulphamerazine, 2 g. initially and 1 to 2 g. eight- to twelve-hourly). Two or three days after pyrexia is controlled and physical signs have moderated, half-dosage may be given for three to six days or until cure appears to be complete.

If a satisfactory response does not occur within three days, a switch should be made to an appropriate antibiotic, or some further line of treatment—e.g. surgical—may be desirable (sulphonamides give poor control when pus is present).

Dosage for children is proportionately lower: under 3 years of age, one-third of the adult dosage, and aged 3 and over, one-half to two-thirds (or 0.3 g./kg. bodyweight daily). Many compounds are available in suspension form, and are particularly useful for children: e.g. mixture of sulphadimidine for infants, B.P.C., 'gantrisin' syrup (and 'cremotresamide', an excellent trisulphonamide preparation).

Parenteral administration is essential at the outset of severe infections, particularly pneumococcocal, streptococcal and meningococcal meningitis, to ensure rapid action. It is also essential in unconscious subjects, or when

uncontrollable vomiting frustrates oral medication. One-third to one-half of the loading dose should be given into a vein. Sulphadimidine sodium injection B.P. and sodium salts of other compounds are available in ampoule form (1 g. in 3 ml.). These should be diluted with 20 to 30 ml. of redistilled water for intravenous use. They may, if necessary, be injected (undiluted) deeply into the gluteal muscle mass, but their alkalinity makes for pain and discomfort. They must not be injected into the theca or other serous cavity.

POORLY-ABSORBED SULPHONAMIDES

These are conspicuously successful in securing intestinal bacteriostasis. Of low toxicity, they are used freely in bowel infections such as acute enteritis, colitis, infantile diarrhœa, bacterial food poisoning and dysentery, particularly Shigella infections, and initially in acute amœbiasis. Succinylsulphathiazole is used in loading dosage (adult) of 6 g., followed by 3.5 g. four-hourly until the number of stools passed daily falls to four; thereafter, a similar amount is given eight-hourly until the motions become solid. Treatment should be limited to fourteen days in any one course. Phthalylsulphathiazole is equally effective in one-half the above dosage.

Of late years the trend has been to combine a poorly absorbed sulphonamide with soluble sulphonamides, with absorbents such as kaolin, or with suitable antibiotics: e.g. streptomycin, neomycin, framycetin. 'Sulphamagna' (activated attapulgite, phthalylsulphathiazole, sulphadiazine, streptomycin) is a typical antidiarrhœal formula. The dose is 2 tablespoonfuls thrice daily. 'Ivax' (sulphaguanidine, kaolin, neomycin) is useful for children. Taylor (1959) reported rapid cure in bacillary dysentery using a combination of soluble sulphonamides with an antibiotic ('streptotriad', containing streptomycin, sulphathiazole, sulphadiazine and sulphamerazine —adult dose, 3 tablets thrice daily). This preparation has also been recommended for the treatment of dysentery carriers. Acute staphylococcal colitis complicating broad-spectrum antibiotic therapy does not respond to sulphonamides; erythromycin or neomycin should be used instead.

Poorly absorbed sulphonamides are an important preoperative routine for elective bowel surgery. This usually consists of succinylsulphathiazole, 20 g. daily by mouth for five days. Phthalylsulphathiazole is preferable as it gives dry stools and is taken in half this dosage. Streptomycin, 1 g. orally, is added on the two days preceding operation and continued intramuscularly for three days afterwards (more effective against enterococci than sulphonamides). Sulphasalazine is reputedly helpful in the diarrhœic phases of ulcerative colitis.

LONG-ACTING SULPHONAMIDES

These are rapidly absorbed and slowly excreted, thus giving prolonged useful blood levels with reduced risk of unpleasant side-effects. They are valuable in preventing infection of the urinary tract during catheter life, and in

cases of relapsing pyelocystitis, provided the infecting organism remains sulphonamide-sensitive. They have proved most helpful for maintenance treatment of skin conditions: e.g. dermatitis herpetiformis, pemphigus, staphylococcal folliculitis and infective granulomas. They are useful also for the prevention and treatment of bronchitic incidents in predisposed subjects. Except for the lessened risk of renal damage, the side-effects are similar to those of other sulphonamides. In view of the high and prolonged blood levels achieved with these drugs, the following dosage should never be exceeded in acute cases: adults, 1 g. on the first day (2 g. in severe infections), followed by 0.5 g. daily; children, in proportionate dosage to bodyweight. The average duration of therapy is six days. The acetyl form is tasteless and acceptable to children (250 mg./20 pound [27.5 mg./kg.] bodyweight on the first day, then 125 mg./20 pound [14 mg./kg.] bodyweight daily.

LOCAL USE

The more soluble sulphonamides have been used on infected skin and connective-tissue lesions. Sulphacetamide forms a non-irritant sodium salt, and 10 to 30 per cent. solutions are much in vogue for ophthalmic, nasopharyngeal and gynæcological work. Powders and creams were formerly applied to infected wounds, ulcers and pyogenic dermatoses, provided purulent discharge was slight. Unfortunately sensitization is common with prolonged local application, a spreading eczematous rash on the surrounding skin being the first sign, followed by generalized dermatosis. Catastrophe may attend subsequent local or general administration of sulphonamides. Indiscriminate topical use is therefore a real danger, and local applications to skin lesions have been largely abandoned.

There may be a cross-sensitivity mechanism in some cases, particularly from previous use of drugs containing a *para*-amino grouping. Cross-sensitivity between procaine and its penicillin salt, saccharin, aniline dyes, rubber accelerators, suntan lotions, *para*-aminobenzoic acid and PAS, which are common pharmaceutical currency today, might well explain some of the toxic phenomena which have been attributed to sulphonamides.

PROPHYLACTIC USE

In comparison with the broad-spectrum antibiotics, the advantages of sulphonamides for prolonged dosage are ready acceptability, convenience of administration, comparative freedom from unpleasant side-effects and economy.

The main indications are for the control of upper respiratory incidents in sufferers from chronic bronchitis, emphysema, asthma, and pulmonary fibrosis. In this role sulphonamides often succeed admirably, provided the treatment extends over six to ten months in each year. Formerly much used for the prevention of hæmolytic streptococcal throat infections in rheumatic subjects, it seems unlikely that the sulphonamides are as effective as peni-

cillin. Hodes (1957), referring to group A β-hæmolytic streptococcal throat infections in children, states that, whilst the bacterial spectra of the sulphonamides and penicillin approximate, yet penicillin with or without sulphonamides is preferable. A sulphonamide should not be used alone in such cases, or in those in which infection has spread from the pharynx and tonsils to the sinuses, middle ear or trachea. The Royal College of Physicians' Rheumatic Fever Committee (1957) recommended 200,000 units of benzylpenicillin, or 125 mg. of phenoxymethylpenicillin, twice daily orally, or 1.2 m.g. of benzathine penicillin intramuscularly each month for five years or to school-leaving age, whichever is the longer.

Prophylaxis of Neisserian and Ducreyian infections is a matter of military strategy in war, and sulphadiazine was found useful (1.5 to 3 g. over eight hours). During endemics of menigococcal septicæmia and meningitis, prophylaxis of exposed adult personnel may be secured with sulphadiazine, 1 g. daily for two to four days, with a proportionate reduction for children. Sulphonamide prophylaxis of urinary-tract infection has already been mentioned.

Most of the prophylactic work has been based on sulphadiazine and sulphadimidine, dosage (0.5 g. daily for five days in each week), but the newer long-acting preparations appear to have great merit in this connexion, and are already reviving interest in sulphonamide-prophylaxis generally. Lepper and his colleagues (1957) gave sulphamethoxypyridazine, 30 mg./kg. daily, to patients in a rheumatic-fever home. All remained free of throat streptococci, and serum levels were superior to those following sulphadiazine. This compound was given for prophylaxis or cure of pyuria by Walker and Hamburger (1957), with excellent effect on the *E. coli* content of the urine, but Proteus and Aerogenes persisted. Current prophylactic dosage schemes for sulphamethoxypyridazine and sulphadimethoxine are 0.5 to 1 g. on alternate days.

Combinations of long- and short-acting sulphonamides have recently become available ('dosulfin', 'bimez'). Curative dosage initially is 4 tablets daily, reducing to 2 tablets daily. They are reputed to be very effective also in prophylaxis of upper respiratory, bronchial and urinary infections (dosage 0.5 g. daily).

TOXIC EFFECTS

Headache, depression, nausea and vomiting.—These are rare with intelligent use of the preparations currently in favour, although occasional patients show idiosyncratic intolerance. Heavy dosage and re-treatment schedules are more likely to cause gastric upset. Crushing the tablets in milk should be tried and a liquid preparation may be better borne. A few doses of cyclizine by mouth or subcutaneously will also help.

Drug fever.—This usually presents after seven to ten days' treatment. An obviously improved and well patient showing only pyrexia should raise suspicion of this complication. Cessation of therapy is essential.

Skin rashes.—These are generally morbilliform; if therapy is stopped immediately, they rarely progress to generalized exfoliative dermatitis. Occasional instances of necrotizing arteritis, erythema nodosum and polyarteritis nodosa have been reported—mainly following sulphathiazole administration. Contact dermatitis may follow local sulphonamide application. A skin reaction is an absolute bar to future sulphonamide therapy. Careful watch should be kept on the blood count of patients showing dermal side-effects.

Blood dyscrasias.—These include leucopenia, agranulocytosis, aplastic anæmia, and thrombocytopenia. They are very uncommon with present-day therapy (the incidence with sulphadiazine, for instance, is less than 0.1 per cent.). They are late manifestations (10th to 30th day of full dosage). Serious degrees of hæmolytic anæmia are rare, but mild cases are common after prolonged heavy dosage. Acute hepatitis may complicate, also purpura. With prompt detection (routine blood counts), blood transfusion and substitution of antibiotics, recovery is usual.

Renal damage.—The most common complication. With sulphamerazine some degree of renal irritation (microscopic bleeding) occurs in 4 per cent. of cases; with sulphadiazine the incidence is 2.5 per cent.; with trisulphonamide tablets B.P.C. it is nil. Careful and sparing dosage is essential in patients who show reduced renal function. Adequate fluid and alkali intake should accompany heavy dosage (including parenteral). The urine should be examined regularly for albumin; if present, blood and sulphonamide crystals are sought for microscopically. In the case of oliguria, sulphonamide administration is stopped immediately and the fluid and bicarbonate intake is increased—by vein if necessary. Irrigation of the renal pelves by cystoscopy will clear severe cases. If evidence of nephrotoxicity supervenes, a Bull-Borst regime must be instituted at once. Extensive renal upset precludes future sulphonamide therapy.

Central and peripheral nervous system damage.—Confusional psychoses, peripheral neuropathies and loss of libido are almost unknown since sulphapyridine and sulphathiazole became unfashionable. Many cases tended to be transient and reversible.

CONCLUSION

The clinical development of sulphonamide therapy was overshadowed by the dramatic and most fortunate wartime debut of penicillin. The series of potent antibiotics which has since become available has tended to push the sulphonamides still further into the background. The relative virtues of the two groups are therefore still imperfectly known, and a huge backlog of research must be completed before precise and final judgment becomes possible.

Domagk's discovery of the clinical virtues of sulphonamides, however, should rank with Ehrlich's work on the arsenobenzenes. Recent important

advances in sulphonamide products serve as a reminder that the pharmacological world continues to be intrigued by the intrinsic possibilities of these drugs. Every medical practitioner should therefore count them worthy of a place in his personal pharmaceutical armamentarium.

A practical illustration of contrary attitudes was noted in a medical journal recently. An article on the drug treatment of pneumonia in adults contained no reference to sulphonamide therapy, whereas in the next issue a pædiatrician, dealing with the same subject in children, led off with the forthright statement that 'sulphonamides are the first choice'. *Ex ore infantium et lactentium*. . . .

SUMMARY

The principles governing sulphonamide administration may be recapitulated thus:—

Therapy should rarely extend over more than seven to ten days. If in acute illness a good response is not evident after three days' full treatment, eventual success is unlikely and the case should be carefully reconsidered.

Fluid intake must be adequate: 4 to 6 pints (2.25 to 3.5 litres) daily for adults. Double these amounts must be ensured in tropical climates.

An alkaline supplement (sodium citrate or bicarbonate 1 to 2 g.) should accompany each dose of the sulphonamide.

The urinary output must be watched and a test for albumin made daily. The leucocyte count should be checked regularly when liberal or prolonged dosage is being given.

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CALLING THE LABORATORY

XIII.—THROAT SWABS

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THE throat swab—it requires no description—is the main tool used for transferring secretions from the throat to the laboratory for microscopic or cultural examination. This is done to determine the etiology of a throat infection or to detect carriers of pathogenic bacteria, particularly diphtheria bacilli or hæmolytic streptococci. Apart from examining throat swabs, the diagnosis of throat infections may also be assisted by taking serum or blood films when infections such as glandular fever or pertussis are suspected.

INDICATIONS FOR SWABBING

Diphtheria.—In the first half of the twentieth century the throat swab was used primarily to obtain material for the bacteriological diagnosis of diphtheria. Until mass immunization of the population made diphtheria a rarity the bacteriologist saw positive cultures every day. Now he may not see one in a year. A practitioner sees even fewer cases. Nevertheless, as a few, usually small, outbreaks still occur every year, diphtheria must still always be borne in mind and swabbing be done in any case of severe sore throat, especially when there is exudate or possible membrane in the throat, much systemic disturbance or obvious adenitis.

Healthy carriers of diphtheria bacilli are now found only in connexion with cases or outbreaks. When cases have been detected energetic mass swabbing—nose and throat—of all possible contacts is essential in an attempt to eradicate completely the focus of infection. Each person needs to be swabbed three times at intervals of at least two or three days. No swabbing should be done within forty-eight hours of receiving chemotherapy. Convalescent cases and carriers cannot be regarded as clear of infection until they have been swabbed similarly.

Streptococcal infections.—Recent surveys (e.g. Chapple *et al.*, 1956) show that hæmolytic streptococci are found in 40 to 50 per cent. of cases of sore throat. They also indicate that it is impossible to distinguish streptococcal sore throats from others clinically. For an accurate diagnosis bacteriological examination is therefore essential. This may be useful in deciding a doubtful case of scarlet fever or when in doubt whether to use chemotherapy. As hæmolytic streptococci are found not uncommonly in healthy persons, especially children, the streptococcus isolated from a sore throat may be unrelated to the illness but this is unlikely if a heavy growth is reported.

Because hæmolytic streptococci may be widespread in a community and yet cause little illness, it may not be worth while trying to eradicate them.

Sometimes, however, streptococcal sore throats may be occurring in sufficient persons over a sufficient length of time to demand action. It may then be thought necessary to do mass swabbing of the community involved, to determine the extent of the infection and the type of streptococcus responsible for the outbreak. In dealing with these outbreaks it is essential to swab the nose as well as the throat, for it has been shown that the nasal carrier is commonly the one who spreads the infection.

Vincent's infection.—The laboratory will normally make a smear from the swab and examine for the spirochætes and fusiform bacilli of Vincent's infection. It should be particularly suspected when exudate, sloughs or ulceration are seen in the throat or mouth. More satisfactory smears will be obtained (especially from small ulcers) if made at the bedside. A similar procedure is used in dealing with suspected thrush lesions.

Pertussis.—Cultural examination is valuable in that it may enable diagnosis to be made before the typical whoop is heard, at a stage when chemotherapy may be useful. This also makes early isolation of the patient possible. The use of the per-nasal swab and new types of laboratory media have greatly increased the reliability of the laboratory diagnosis of pertussis.

Virus infections.—A substantial proportion of sore throats are probably due to virus infections such as the common cold and influenza. None of these can be diagnosed routinely in the laboratory, but in special circumstances some laboratories might be willing to help if approached. In many centres practitioners cooperate with virus workers in identifying cases of influenza for epidemiological and research purposes.

PRACTICAL CONSIDERATIONS

Laboratory facilities.—In England and Wales the Public Health Laboratory Service and in some areas the local hospital laboratory will provide outfits and report on swabs sent in to them. In Scotland a similar service is provided by university departments or hospitals. A newcomer to a town should inquire from the health department about the local arrangements.

Outfits.—The outfit provided consists of a sterile swab contained in a test-tube, along with a box, application form and envelope bearing the address of the laboratory. With suspected pertussis a special per-nasal swab should be requested from the laboratory.

Swabbing technique.—Swabbing should be done if possible before treatment has begun and certainly not shortly after a local disinfectant, gargle or lozenge. If the patient is under chemotherapy this should be stated.

Most doctors will know how to immobilize a small child. He sits on his mother's knee facing the doctor. The mother grips the child's legs between her knees, fixes both his arms by passing her right arm round the front of the child and gripping his left arm. Her left hand she places on the child's forehead and draws it backward. Under good illumination from a hand torch, or with the patient facing a good light, the posterior part of the tongue is firmly depressed. After noting any abnormal appearances the swab is

rubbed firmly over the tonsils and posterior laryngeal wall. Special care, perhaps with the aid of forceps, is taken to remove a portion of any exudate or membrane present. In a suspected case of pertussis a special per-nasal swab is used.

This consists of a slender wire carrying a small cotton-wool swab at the end. This swab is a more slender instrument than the normal throat swab and is pushed along the floor of the nose to the nasopharynx and then rotated. After withdrawal the swab is plunged into the special medium at the bottom of the swab-tube.

Form filling.—It is important to fill up all the particulars on the application form fully. There is a good reason for asking for each item of information. A completely filled form indicates to the bacteriologist the types of examination that will be most valuable and the seriousness of the case, and helps him to interpret his results. Information on the form may also provide valuable epidemiological information later.

Transmission of swab.—The longer the delay in a swab reaching a laboratory the fewer organisms will be grown from it. If possible it should be delivered by hand— a relative can usually do this. In large towns delivery may be facilitated by depots in the centre of the town, where swabs can be left. The laboratory will be able to advise on the local arrangements, particularly about the arrangements for the reception of swabs in the evenings and at weekends. Where the laboratory is at a distance swabs may have to be posted. More reliable results may be obtained with these delayed swabs if the laboratory is able to provide swabs pretreated with serum (Rubbo and Benjamin, 1951). Arrangements may also be made for urgent specimens to reach the laboratory the same day by sending them by passenger train marked 'to be called for' and telephoning the laboratory about the time they are arriving. Bus transport may also be used similarly.

Reporting specimens.—The laboratory will probably telephone any positive results, but if there is doubt about this a request for a telephone message can be marked on the form. Film results should be available in not more than twenty-four hours; preliminary culture results in twenty-four to forty-eight hours. Tests for grouping or virulence may not be available for several days.

INTERPRETATION OF RESULTS

A positive result for diphtheria bacilli, hæmolytic streptococci or Vincent's organisms in the presence of an acute sore throat is best assumed to mean that the organism is the cause of the condition. The significance of other potential pathogens—*Staph. aureus*, the pneumococcus, *H. influenzæ*—is less certain. These organisms occur commonly in small numbers in healthy throats, but their presence in large numbers may indicate that they are the cause of a sore throat or sinus infection. *Candida albicans* may appear in throat cultures, but no significance should be attached to this unless the organism is so abundant that it is found in numbers in direct smears of the throat.

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PRINCIPLES OF REHABILITATION

I.—WALKING AIDS

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The purpose of this series of articles is to deal with practical ways of assisting or restoring functions impaired or lost as the result of an accident or disease. In these days there are many books and pamphlets showing innumerable aids and gadgets which are good, indifferent, or bad. So many are shown that confusion in the choice of particular gadgets most suited

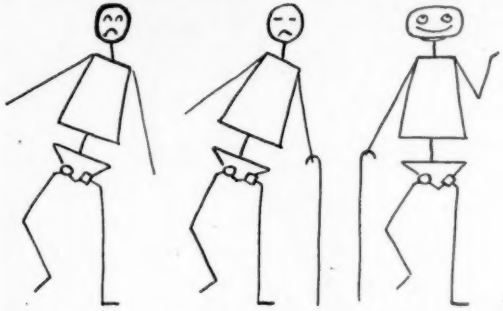

Fig. 1.—Pain in one hip and the correct use of a walking-stick.

to the patient inevitably occurs. By discussing the principles involved it is hoped that it will be made easier for the family doctor to select the aid most suitable for the individual patient.

As we are dealing with the locomotor system, locomotion, or walking, which the late Professor James Whillis used to describe as a controlled falling, will provide a good starting point. Aids to this function vary from a walking-stick to a spinal carriage.

Aids used by the upper extremity consist of:—

(1) (a) Walking-sticks
(b) Quadrupod walking aids
(c) Walking-frames
(2) Elbow crutches
(3) Full-length crutches

WALKING-STICKS

These require a good grip, reasonable strength of arm and forearm, and freedom from joint pain in the upper extremity. Their use will vary from aiding balance to partial weightbearing—as in the quadrupedal type of walking aid. They are most effective when the length chosen is such that

it enables the patient to use it with the elbow joint at 180° to 150°.

There is one point which should be borne in mind when dealing with pain in one hip-joint. When standing on one leg, the pelvis is tilted to the weightbearing side, mainly by the action of the gluteus medius. This produces a triangle of force which, acting through the neck of the femur, produces a down thrust which may be up to three times the actual weight.

FIG. 2.—Simple attachment to handle of walking-stick to leave hand free for actions such as opening doors.

By using a stick or crutch on the good side, much relief is afforded to the other hip, since the gluteus medius does not have to contract to stabilize the pelvis (fig. 1).

Figure 2 shows a simple way of keeping the handle of the walking-stick near to hand, but leaving the hand free for opening doors and the like.

QUADRUPOD WALKING AIDS

These give more stability than a walking-stick and produce the same effect as if the patient had a small coffee-type table of convenient height on each side of him. Certain patients feel more confident with this type of walking aid than with the walking-stick but, as these aids have a base approximately 14 inches x 7 inches (35 cm. x 17.5 cm.), they are not convenient to use in a room which is full of furniture. The tripod type of walking aid, which is

usually a misnomer for the quadrupod, is less suitable and less popular with the majority of patients.

THE WALKING-FRAME

This is virtually a four-legged support, the feet of which end in either crutch rubbers (fig. 3a) or wheels (fig. 3b), and with which the patient stands either within the actual base of the frame or just behind it. Another

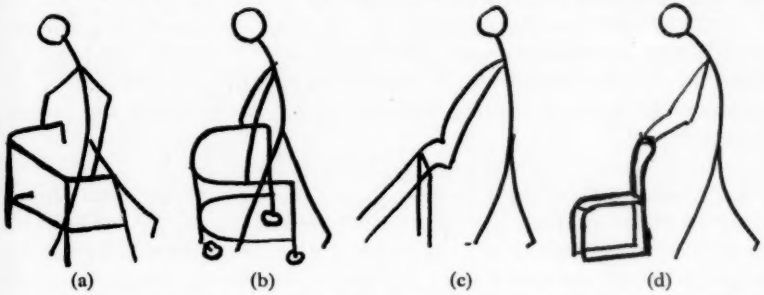

FIG. 3.—Walking-frames: (a) On legs, (b) with wheels, (c) hinged, and (d) tubular stacking chair.

variety of this type of walking aid is a type similar to those in which the two back legs are hinged on to the two front legs and the apparatus is walked along by opening and closing these legs (fig. 3c). A useful thing to remember is that an ordinary metal tubular stacking type of chair pushes along quite

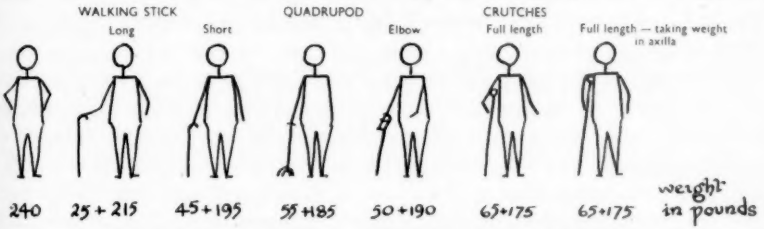

FIG. 4.—Weight distribution of different forms of walking aid.

easily on a carpeted floor (fig. 3d). A very good idea of how useful a walking-frame will be can be obtained by testing the patient out on such a chair, and quite often such a chair will be found to be all that is needed.

The choice of the variety of walking aid depends upon the degree of disability and the skill of the patient using it. Generally speaking, those with rubber-capped feet are easier to manage as they do not give the patient the running-away feeling often experienced with the wheeled variety.

THE ELBOW CRUTCH

This requires a good grip to transmit some of the weight but does not require so much strength in the wrist, as the forearm extension of the crutch improves the leverage effect.

FULL-LENGTH OR SHOULDER-TYPE CRUTCHES

These require even less strength in the wrist than elbow crutches. It should be borne in mind that the top of these crutches is intended to be gripped between the upper arm and the chest wall and not to bear weight in the axilla. Heavily handicapped people, however, may only be able to walk by axillary weightbearing on their crutches and this may have to be permitted for short distances, such as going about the house.

Figure 4 illustrates the situations arising when various walking aids are used. These experiments were carried out with a patient weighing 240 pounds (109 kg.) and the weight distribution or lessening produced by the various aids was put down as separate figures according to the results obtained.

WEIGHT REDUCTION

Finally, when attempting to relieve pain in a weightbearing joint, do not omit the most obvious thing and that is to reduce the weight which it has to bear when the patient is overweight. With most patients this is an extremely difficult job owing to the fact that all overweight people invariably assert most vehemently that they 'scarcely eat a thing'.

REVISION CORNER

BAT EARS

THE term, 'bat ears', has come to mean prominent ears. When faced with a child with very prominent ears there are many factors to be taken into consideration in deciding whether or not the ears require correction. First of all it is not easy to say when a bat ear becomes a deformity. A count in any public school in England today will reveal that one in eight of the boys have prominent ears, which are in fact perfectly normal ears. We were not all made in the same pattern; some people look equally peculiar when their ears are stuck to the side of their heads. Such terms as 'elephant ears', 'red sails in the sunset', and 'Dumboesque' have been used to mock and deride small boys with these very prominent ears. According to the character of the boy in question so is his response. The ordinary boy will react violently and possibly with his fists. Others retreat into a corner and find themselves unable to compete with the deriding jeers of their fellows.

The first rule to be borne in mind when dealing with such a boy is to remember that it is not good practice to operate on children just to please over-anxious parents. If a child with prominent ears is brought to see his doctor and he has never been teased at school and, in fact, shows no untoward reaction to the fact that he has a slight physical abnormality, then I can see no indication for submitting that boy to a surgical operation. If, on the other hand, a young boy comes with his parents and states quite openly that he would like to have his ears corrected because he finds that ragging at

school is getting him down, then there is quite a strong indication for operation.

CLASSIFICATION

Bat ears have been divided into three main categories. First of all the ear which is merely prominent and shows none of the abnormal configurations of the succeeding two groups. In such an ear a helix, an anti-helix ridge, a normal concha and the general configuration of the normal ear (fig. 1) can all be recognized. This is probably the commonest type of prominent ear and ragging may take place, but there is not very much about the appearance of such a boy which is going to stand him in bad stead at a later age, and this is not a true deformity.

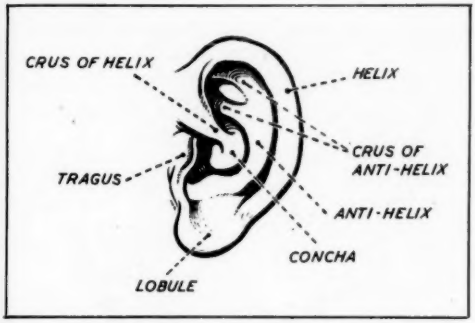

FIG. 1.—The normal configuration of the external ear.

The second group is that group of ears in which the anti-helix ridge is only just visible and may even be absent, so that the ear is turned forwards and may even be turned downwards and forwards. This really constitutes a deformity, and if the boy feels that he would like an operation, I would have no hesitation whatever in offering him the benefits of surgery.

In the third group is a strange collection of ears of varying sizes and shapes, which may not even be normally placed on the side of the head. For instance, one ear may be as much as an inch lower than the other one. The other ear may be a little crumpled thing: in other words, there is a marked deformity with an asymmetry between the two ears which is a handicap to any child who wishes to go through life where appearance in our modern civilization appears to be so important. In this group there is a small sub-group of patients who may have an associated malformation of the genito-urinary tract. The relative rarity of this sub-group is shown by the fact that in the whole of the children's practice of the Plastic Unit at the Queen Elizabeth Hospital for Children and at St. Thomas's Hospital, we have only been able to find one such case amongst our ear deformities over a fourteen-year period. Nevertheless, in the case of a small boy with peculiar ears who has symptoms referable to the genito-urinary tract, it is worth considering early pyelography.

Bat ears may be inherited, but a family history is by no means the rule.

TREATMENT

Unfortunately there is no prophylactic, or conservative treatment. There are many mothers who strap the ears firmly back, who design little caps to hold

the ears flat to the side of the head, and who suffer a great deal of anxiety in trying to ensure that the ears become less prominent as the child grows older. In fact, none of these measures makes the slightest difference and mothers are advised to stop worrying about the child until such time as he is older and has to start worrying for himself.

SURGICAL TREATMENT

The best results from operation are to be seen at 8 or 9 years of age, when the ear has reached full maturity and no further change is likely to take place in growth or shape.

The principles of the modern operation (fig. 2) for bat ears are not only to pin the ear to the side of the head, for which many operations were

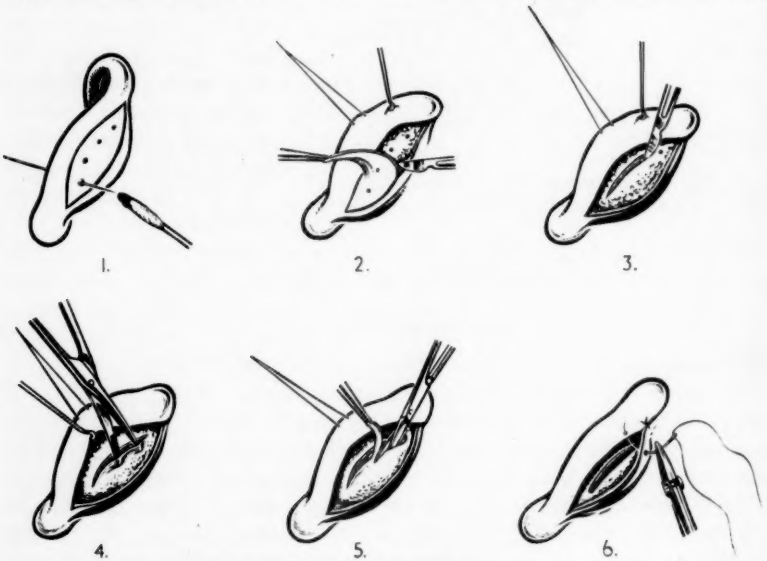

FIG. 2.—The operation for correction of the bat ear deformity.
(1) Ellipse of skin marked out on the back of the ear. Needle inserted across the ear —touched with Bonney's Blue and withdrawn again. Points along the line of the anti-helix ridge are chosen for these insertions.
(2) Ellipse of skin removed.
(3) Cartilage incised along the line of the dots.
(4) Soft tissues freed on the anterior or outer aspect of the ear.
(5) Strip of cartilage removed along the line of the anti-helix.
(6) Skin incision sutured.

designed in the past, but to try and reproduce an anti-helix ridge where such a ridge is absent or only rudimentary.

The operation is done under general anæsthesia, and both ears are dealt with at the same session. It is easier to do the bad ear first and see how far that will go back, before tackling the other, which must be made to match the severe one.

The first move in the operation is to mark out the line of the anti-helix ridge. If this ridge is rudimentary, the ear is folded back and the ridge reproduced with

the fingers. In order that the marking should penetrate to the cartilage, a straight needle is run through the ear from side to side, the tip wiped with Bonney's Blue on a cotton-wool swab and the needle withdrawn. This may require some six punctures along the line of the ridge, and later a trace of blue is found in the cartilage itself. Having marked out this ridge, an ellipse of skin is removed. The worse the deformity the more skin must be taken. The blood vessels are picked up and tied, and the cartilage is then exposed to view with the blue dots in it, representing the line of section. A knife is taken right through between these dots from top to bottom of the ear, and the skin on the front of the ear is freed very gently along

FIG. 3.—Bat ear with absent anti-helix ridge (a) before and (b) after treatment.

the margins of the cartilaginous incision. The ear is then turned back into its normal position again so that an estimate can be made of how much of this cartilage should be trimmed away. On looking at the outer aspect of the ear, the new anti-helix ridge will probably stand out too prominently. There may also be a tendency for the ear to flop forward, and accordingly (and only experience can tell at this stage) the ear is turned back and, with a pair of scissors, a strip of cartilage is removed running down along the margin of the cartilaginous incision which is closest to the head.

If enough cartilage is not taken the first time, then more cartilage will have to be taken until not only does the ear lie comfortably and show no sign of wanting to relapse, but it also shows a reasonable anti-helix ridge without too much prominence about it. It is not necessary to suture this cartilaginous incision.

It then remains only to sew up a rather difficult curved wound in the skin—one margin of which is longer than the other—either with interrupted stitches, usually end-on mattress in type or with a subcuticular stitch. In order to save children

the removal of very difficult stitches from the back of a rather tender ear, I personally have taken to using 20-day chromic catgut.

At the end of the operation, firm dressings are placed on each ear, flavine and paraffin sometimes being packed carefully into all the interstices and a little dressing behind the ear to prevent it from sticking to the side of the head. Crêpe bandages will complete the pressure, and in this way a hæmatoma is avoided.

AFTER-CARE AND COMPLICATIONS

The *after-care* of this operation is simple. The child stays in bed for forty-eight hours. The ears are then looked at, and if normal and satisfactory, the patient can leave hospital with a bandage on. The wounds should be healed in a week, but a brisk turn over in bed during sleep could easily cause a disruption. Accordingly, it is wise policy for the patient to keep the ears bandaged at nights for a further fortnight. The results in a typical case are shown in fig. 3.

Complications.—Only two complications have been met with to date. (a) Very mild infection occurred in one case, which reacted at once to parenteral penicillin. (b) In two patients operation has had to be repeated owing to the persistence or recurrence of the deformity. In one of these an inadequate amount of skin had been removed at operation; in the other relapse had occurred with growth of the ears subsequent to operation performed at too early an age.

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NOTES AND QUERIES

A Snail-Eating Child

QUERY.—I have been asked for my opinion on a child aged eighteen months who delights in eating the small snails that she finds in the garden under stones. She crunches these up with an ecstatic expression on her face. She has no symptoms of indigestion or psychological maladjustment: she just enjoys small crunchy snails. We are in a part of the country well-known for its population of (so-called) Roman snails. A neighbour's child did the same thing until she grew out of the habit: the only after-effects being that she thoroughly enjoyed French snails and frogs' legs on her recent French holiday.

Can any complications of infection or infestation attend this enjoyable habit? Would any treatment short of smacking help cure it?

REPLY.—My pathologist, to whom I turned for help with this question, referred me to Stitt, Clough and Clough (1945). If the snails in question are water snails, it seems that there is a remote possibility that the larvæ of the fluke (*Fasciola hepatica*), which causes 'liver rot' in sheep, might be ingested, but the risk seems slight. From the ovum, a free swimming larval form enters the body of a water snail, there to develop into *rediæ*; these develop into *cercariæ* which leave the mollusc to swim in water. It seems that the sheep is usually infested by eating the encysted cercariæ upon grass or through drinking water containing them. Many children eat snails, many more eat grass; *Fasciola hepatica* infestation in man is very rare and the symptoms reported in most cases are mild. The mollusc host of this parasite (*Lymnæa truncatula*) is a common snail of ponds and streams; it has a delicate fragile shell with a pointed spire.

Pica is a familiar problem to pædiatricians for many young children indulge in the practice. The analogy between pica in children, the perverted appetites of some pregnant women, and the behaviour of adrenalectomized rats (which may maintain themselves in water and electro-

lyte balance if given free choice of suitable solutions) has been too much stressed. Starving children may eat anything and everything but there are no good grounds for supposing that the child who eats snails is seeking to correct some vitamin or trace-element deficiency. The reiterated opinion expressed in standard texts to the contrary, in my own experience pica is not confined to sub-standard homes and malnourished and emotionally deprived children. Indeed circumstances are sometimes so much the reverse that one surmises that the habit represents the over-cossetted child's struggle to be independent: the alarm and dismay caused by eating some particularly obnoxious (to adults) substance may create such a fuss that the child feels more than compensated for a nasty taste.

In this connexion one may comment that toddlers do seem to have a peculiar sense of taste (raw snails *may* taste nice: one notes that the infant under discussion crunches the snails 'with an ecstatic expression on her face'). Toddlers will eat, chew and swallow numbers of aspirin or ferrous sulphate tablets and will drink kerosene and turpentine: to paraphrase Dr. Johnson, they may not taste well, but you are surprised to find them eaten at all.

Smacking would be my own treatment for my own child in circumstances such as these (and I would quote Samuel Johnson in my defence) but it is not the only cure. Gentle scolding would probably be effective: 'Mummy says you mustn't'. Nagging and arbitrary condemnation based on insufficient knowledge should be avoided: 'Dirty, nasty, horrid snails' may be manifestly untrue to the child who relishes them.

The average child of eighteen months has an urgent developing need to explore, to experiment and to experience, to test and to taste; the parents should review their handling of this child to satisfy themselves that their home provides adequate opportunities to meet this need.

Reference

Stitt, E. R., Clough, P. W., and Clough, M. C. (1945): 'Practical Bacteriology, Hæmatology and Animal Parasitology,' London.

R. M. MAYON-WHITE, M.D., PH.D., M.R.C.P., D.C.H.

Why Hang Game?

QUERY.—I am wondering if you can help me with a problem which is really of no medical importance but has puzzled me for some time. It is this. One normally hangs game, such as pheasant, partridge and hare, for quite a while, until it is fairly 'high' before cooking. To most palates this is extremely tasty fare and has no ill effects. A domestic fowl, duck or goose left for such a time becomes tainted and unpleasant and I believe will cause abdominal pains, vomiting and diarrhœa.

I am interested to know what are the pathological or bacteriological changes which take place and which render the one meal appetizing and pleasant and the other offensive.

REPLY.—Game at its best—properly hung, cooked and served—contains more protein than common meats. Roast grouse, pheasant and hare have a protein content of about 30%; roast partridge and venison do even better—35%. Domestic animals are generally inferior in this respect: e.g. beefsteak and roast mutton, 25%; roast farmyard duck, 23%. The hard-working muscles of wild animals seem to contain more elastic protein, with less water and glycogen, than those of leisured beasts.

Dead muscle is rendered palatable and digestible by *autolysis*, which is primarily due to the action of surviving proteolytic enzymes within the tissue. These enzymes work best in an acid medium, like pepsin in the stomach. The acid is provided by the anaerobic breakdown of muscle glycogen into lactic acid—a normal process in severe physical exercise. This may explain why an animal freshly killed and eaten immediately after a hunt is reputedly more tender than one quietly killed in a slaughterhouse. Muscle if not eaten at once undergoes *rigor mortis* caused by coagulation of the proteins which makes the food tough. The toughest game of all is the wing of a woodcock or the leg of a partridge, killed the day before. The process of autolysis breaks down some of the proteins into peptides or even their constituent amino-acids. One of these, glutamic acid, has a pleasant meaty taste, but the sulphur-containing amino-acids (cysteine and methionine) can yield sulphides on autolysis, accounting for the smell of a stale egg. No sensible person leaves an egg to hang.

The palatability of a meat probably depends upon the amino-acid pattern of its proteins and the time allowed for autolysis. Game—low in glycogen but high in protein—takes its time.

There is the further factor of water which is less in the muscles of game animals than in the flesh of fish or young mammals (e.g. veal). Bacteria grow freely in dilute organic solutions. They are normally present in small numbers in most living tissues, but their reproduction is suppressed until the body dies. When this happens, they multiply exceedingly with various consequences. They may assist in a benign autolysis or, alternatively, produce both a vile smell and a virulent toxin as in the case of the clostridiæ. Every animal has its own symbiotic bacteria which—after death—may either enhance or vitiate the nutritional value of its meat. This perhaps explains why we gralloch a stag

on the spot, yet confidently serve woodcock with entrails intact after a fortnight's hanging.

A. P. MEIKLEJOHN, D.M., M.R.C.P.

Cheese and Penicillin Sensitivity

QUERY.—My daughter returned from Dusseldorf after a visit to her sister where she literally 'ate pounds' of gorgonzola cheese. The skin (face, back, chest and shoulders) broke out in a pustulant angry rash. As she is very sensitive to pencillin, it occurred to me that this rash might well be due to the penicillin in the cheese; this view seemed to be supported by the fact that since her return she has eaten no cheese at all, and the rash has almost completely disappeared.

I would be most grateful for your expert's views on this matter.

REPLY.—Four cases of penicillin-induced dermatitis, resulting from the consumption of milk products, have lately been reported from the U.S.A. (Zimmerman, 1959). In two cases the dermatitis followed the consumption of Roquefort cheese. That the skin condition was due to penicillin was proved by the response to penicillinase. All gave a history of previous sensitivity to penicillin.

It is apparently not the natural mould in the cheese that is to blame, but rather the increasing use of penicillin by dairy farmers for treating the common mastitis of cattle. The penicillin is introduced directly into the udder and easily contaminates the milk. Cheese-makers are inconvenienced by this practice, as are some consumers of their product, because the penicillin interferes with the normal ripening of the cheese.

Zimmerman, M. C. (1959): *Arch. Dermat.*, 79, 1.

A. P. MEIKLEJOHN, D.M., M.R.C.P.

Coronary Thrombosis and Manual Labour

QUERY.—I have a male patient, aged 50 years, who has recently had a coronary thrombosis. He has recovered with no complications, and there are no symptoms or signs of heart failure eight weeks after the incident. He is a driver of heavy vehicles and his work involves a fair amount of heavy manual labour. What are his chances of returning to this job after a prolonged convalescence?

REPLY.—It is usual for men who are known to have made a good recovery from coronary thrombosis to resume driving their own private cars three months after the attack. Residual mild angina does not preclude it. Similarly the owner of a hire cab might reasonably be allowed to drive. But such concession should not be extended to drivers of heavy vehicles even after more prolonged convalescence, and heavy manual labour is permanently contraindicated.

C. J. GAVEY, M.D., F.R.C.P.

Gravitational Swelling in Paraplegia

QUERY.—I have a patient whose lower limbs have been totally paralysed since she had poliomyelitis about seven years ago. Her feet and ankles are swollen and usually cold in spite of warm shoes. What possible complications may ensue (such as ulcers) and how may they best be prevented?

REPLY.—The swelling of the feet and ankles in this case is almost certainly gravitational. It will be greatly helped by some arrangement whereby the patient can lie down with the feet and legs at least as high as the level of the heart for half-an-hour three times a day. Firm elastic stockings will also be helpful. With regard to the cold, the mistake is often made of trying to keep the legs warmed, but the proper method to warm the legs, of course, is to overheat the body by some artificial means such as an electric blanket in the chair, or wearing extra body clothes. The paralysed legs should be insulated so far as possible with rugs but should not be brought into contact with hot water or the radiation of a hot fire, and the low temperature should always be counteracted by heating the body and not the limbs.

With these simple measures no complications need be expected.

W. RITCHIE RUSSELL, C.B.E., M.D., F.R.C.P.

Visual Standards for Driving

QUERY.—(1) I should be grateful if you would inform me whether a man whose vision is 6/6 (L), 6/30 (R), would in this respect be eligible to hold a P.S.V. driving licence. (2) What are the required visual standards?

REPLY.—(1) Yes. (2) 6/12 in one eye, 6/36 in the other—with or without glasses.

F. E. CAMPS, M.D.

Vegetarianism and Anæmia

QUERY (from a reader in Ceylon).—I was interested to read your expert's answer regarding vegetarian diets (*The Practitioner*, July 1960, p. 117). I note that he says that 'many people who keep to such a diet ["vegan" diet] develop anæmia and other signs of deficiency . . . '. Why *many* people and not *all?* Here in Ceylon, with a mainly Buddhist population, a 'vegan' diet is not at all rare (e.g. on religious grounds). I have noticed, however, that, although the vast majority of these people who take 'vegan' diets are grossly anæmic, there are some who appear in very good condition and

are long-lived. How can this be accounted for? Are there any vegetable substitutes that could furnish the iron requirements of the body satisfactorily?

REPLY.—It is not because of a deficiency of iron that vegetarians tend to become anæmic, but because of a deficiency of vitamin B_{12} (cyanocobalamin) and possibly other nutrients which are found in animal foods. It is indeed true that not all vegetarians become anæmic, and it is supposed that this is because some vitamin B_{12} (and other nutrients) may be synthesized by micro-organisms in the alimentary canal, and then absorbed into the blood stream. Different individuals might then differ both in the amount of such factors synthesized, and in the proportion of them which they absorbed. This would explain why some vegetarians become anæmic, and some do not.

PROFESSOR JOHN YUDKIN, M.D., PH.D., M.R.C.P., F.R.I.C.

Xerosis Epitheliasis

DR. K. R. KRISHNAN (Coimbatore, Madras Province) writes:—The condition described by your Singapore reader (*The Practitioner*, July 1960, **185**, 115), i.e. xerosis epitheliasis, is commonly met with among the poor in Southern India, particularly children. Out of 1,130 boys examined in municipal schools here, it was found to occur in 54 (4.8%). Almost total lack of proteins in the diet of these children, more than anything else, seems to be responsible for this condition. In this connexion I would like to refer your reader to an article by Bagchi *et al.* in the *Journal of the Indian Medical Association* (November 16, 1959, **33**, 401). The exciting cause appears to be dust irritation, for the lesion occurs symmetrically, and often in both eyes, in the exposed portion of the bulbar conjunctiva. The predominant occurrence of chronic upper respiratory catarrh in association with this condition also lends evidence to this view. In the 54 cases cited, chronic upper respiratory catarrh was found in 17, toad skin in 7, dry skin in 2, angular stomatitis in 6, refractive error in 6, dental caries in 2, scoliosis (postural) in 2, wart in 1, keloid in 1, and anæmia in 1.

The role of vitamin A deficiency in etiology is by no means insignificant and it is well to remember that computation of vitamin content of actual diets without reference to the method of cooking is erroneous. I wonder whether South Indian culinary art, which is essentially prolonged boiling and frying, will leave any vitamin in the finished product.

The treatment, which is protracted and perhaps unrewarding in many an instance, consists of:—

(1) Provision of more than adequate quantity of protein of high biological value.

(2) Drastic reduction of rice and other carbohydrates.

(3) Multivitamin supplement in addition to liberal ration of vitamin A.

(4) And last, but not least, avoidance of a dusty atmosphere and overcrowding.

PRACTICAL NOTES

Phenethicillin

THAT phenethicillin potassium is 'an agent of some interesting facets without *per se* representing any great advance in clinical therapeutics' is the conclusion of W. J. Martin and D. R. Nichols (*Proceedings of the Staff Meetings of the Mayo Clinic*, September 28, 1960, **35**, 577), who carried out a comparison of serum concentrations and of antibacterial effects between phenoxymethylpenicillin and phenethicillin potassium in 22 patients. Each patient received 250 mg. of phenoxymethylpenicillin by mouth every six hours for four doses, and serum was obtained for assay and *in vitro* antibacterial testing two hours after the fourth dose. After an interval of at least twenty-four hours the same procedure was carried out for phenethicillin potassium. Although in the majority of patients (18) the mean concentration of phenethicillin in the serum was found to be significantly higher than that of phenoxymethylpenicillin (2.67 mcg. per ml. as against 1.65 mcg. per ml.), with 'so-called penicillin-sensitive staphylococci being used as test organisms, the antibacterial activity of serums containing either preparation was not appreciably different from the activity of serums containing the other'. It was concluded that the chief virtue of phenethicillin potassium appears to be 'as the probable bellwether of newer penicillin fractions of possible clinical application that will be produced synthetically'.

Allergy to Phenethicillin

ALTHOUGH the advent of phenethicillin 'raised the hope that it could be used with impunity in patients who had previously shown allergic reactions to penicillin', cross-reaction tests show that this is not the case, according to L. H. Criep and H. Friedman (*New England Journal of Medicine*, November 3, 1960, **263**, 891). Describing tests in two patients who were

allergic to penicillin G, they found that both penicillin G and phenethicillin cross-reacted on skin testing and passive transfer. Administration of phenethicillin in these two cases resulted in violent reactions requiring emergency treatment in hospital, and scratch tests carried out at a later date in one of the patients gave a marked positive reaction to 1000 units of phenethicillin per ml., a moderate positive reaction to 100 units per ml., and a negative reaction to 10 units per ml.

Sulphadimethoxine in Urinary Infections

SULPHADIMETHOXINE is at least as effective as trisulphonamide for the treatment of acute urinary infections due to sulphonamide-sensitive bacteria and is better tolerated, according to M. C. Lewin (*British Journal of Urology*, September 1960, **32,** 324). These conclusions are based upon the findings in an investigation in which 17 patients who developed acute urinary infections while in hospital were treated with sulphadimethoxine, one of the new long-acting sulphonamides, whilst a control group consisted of 20 comparable patients who were treated with trisulphonamide. The dosage of sulphadimethoxine was an initial dose of 2 g., followed every twenty-four hours by a maintenance dose of 1 g. Sixteen of the 17 patients receiving sulphadimethoxine were bacteriologically and clinically cured, compared with 14 of those receiving trisulphonamide. No side-effects were observed in the patients receiving sulphadimethoxine, but four of those receiving trisulphonamide had reactions (two had rashes and vomiting, and two had vomiting) which made a change of treatment necessary. Attention is drawn to the fact that 'the single daily doses [of sulphadimethoxine] proved popular with both patients and staff'.

Sulphamethoxypyridazine in Urinary Infections

SATISFACTORY results from the use of the long-acting sulphonamide, sulphamethoxypyridazine, in the treatment of urinary infections are reported by J. D. Wargo and his colleagues (*American Journal of Obstetrics and Gynecology*, September 1960, **80,** 490). Of the 174 patients treated, all of whom were in 'a gynecologic-obstetric service', 77 had cystitis, 45 had pyelonephritis, and 52 had an indwelling Foley catheter. Two dosage schedules were used: (a) an initial dose of 1 g., followed by 0.5 g. daily; (b) an initial dose of 2 g., followed by 0.5 g. twice daily. 'Excellent' or 'satisfactory' results were obtained in 70% of the patients with cystitis, and 60% of those with pyelonephritis. 'As anticipated, only 22% of the patients with an indwelling catheter could be proved to have been helped'. The average length of treatment was 3.7 days for the patients with cystitis, and 6.7 days for those with pyelonephritis. Few side-effects were encountered. One patient developed a 'typical generalized sulphonamide rash', whilst in only one patient were sulphonamide crystals found in the urine, and these produced no symptoms or signs. In one patient the white cell count fell from 6,800 to 3,600 per c.mm. after three days, but returned to normal in another three days without discontinuation of the drug. The final assessment is that sulphamethoxypyridazine 'compared favourably with other sulphonamides in the treatment of urinary infections'.

Treatment of Lichen Planus

'DIPASIC' (the *p*-aminosalicylic acid salt of isoniazid) is 'a valuable remedy' for lichen planus, according to J. O'D. Alexander (*British Journal of Dermatology*, October 1960, **72,** 355), as a result of a clinical trial in which the patients were followed up for at least six months, and some for over two years. The dosage of 'dipasic' was 600 mg. daily for six weeks, and 300 mg. daily for a further six weeks. Apart from talcum powder, local treatment was entirely avoided. Of 41 patients treated with 'dipasic', 32 had 'a very good response to treatment', compared with only five of 14 controls treated with a placebo. Four of the treated cases and eight of the controls showed no response whatever. Four of the eight control failures subsequently showed an 'excellent' response to 'dipasic'. An analysis of the results showed that the acute generalized type and the more local chronic type of lichen planus, such as occurs on the wrists and forearms, responded more readily to 'dipasic' than the hypertrophic variety. The 'most remarkable feature' of the results was the rapidity with which itching was relieved: this usually occurred within the first two or three weeks. No side-effects were encountered. The mechanism of action of this anti-tuberculous drug in lichen planus is unknown.

Intrapleural Hydrocortisone

EVIDENCE in favour of the efficacy of intrapleural hydrocortisone in the treatment of tuberculous pleural effusion is adduced by K. S. Mathur and his colleagues (*Tubercle*, October 1960, **41,** 358). Twenty-five cases, which served as controls, were given streptomycin and isoniazid, with aspiration of fluid when this was necessary for the relief of symptoms. Twenty-five other

cases were treated on the same regime, but without therapeutic aspiration even when the effusion was massive; in addition, hydrocortisone was injected intrapleurally: 250 mg. in the first ten patients and 125 mg. in the remainder. In the hydrocortisone group the fever settled to normal in twenty-four hours in 21 patients and within forty-eight hours in two; the remaining two were apyrexial from the beginning. In the control group the fever took two to four weeks to settle to normal in the majority, and never less than one week. A rapid fall in the erythrocyte sedimentation rate occurred in the hydrocortisone group, as compared with a more gradual fall in the control group. The effusion cleared within a fortnight in 18 of the hydrocortisone patients, whilst in the control group no patient showed a similar change in such a short period. In only two of the hydrocortisone group was the absorption of the fluid 'unsatisfactory', compared with 16 of the control group. The results were just as good with 125 mg. of hydrocortisone as with 250 mg. A follow-up, six to twelve months after discharge from hospital, showed that in the hydrocortisone group 16 showed no residual pleural thickening and seven were left with 'slight haze or pleural thickening at the costophrenic angles'. In the control group variable grades of thickened pleura were left in most of the patients.

Ergotamine Inhalation in Migraine

As a result of his experience in a series of 65 patients with 'recurrent vascular headaches', W. G. Speed (*American Journal of Medical Sciences*, September 1960, **240**, 327) concludes that 'a more consistent and rapid response with a smaller dose of ergotamine tartrate is obtained from oral inhalation than from any other route except the more cumbersome subcutaneous and intravenous ones'. The aerosol was delivered by means of the 'medihaler', the concentration of micronized ergotamine tartrate being such that 0.36 mg. was delivered per valve depression. The patients were instructed to use one inhalation immediately on the onset of headache, and to repeat one inhalation every five to ten minutes until relief was obtained, but not to exceed six inhalations per twenty-four hours. 'Excellent' results (i.e. the headaches were controlled in less than 1½ hours) were obtained in 82.6% of the 46 patients with migraine, 84.6% of the 13 patients with histaminic cephalagia, and 66.6% of the six patients with tension headaches. The number of inhalations required for complete relief averaged two to three, ranging from one to six depending upon the severity of the headache. About one-half were relieved in thirty minutes or less. The incidence of side-effects (mainly nausea and vomiting) was 22%, but only two patients gave up treatment on account of these.

Dichlorophen as a Tænifuge

'DICHLOROPHEN, 6 g., given orally without any ancillary treatment, is effective in curing about 90% of infections with *Tænia saginata*,' according to D. R. Seaton (*Annals of Tropical Medicine and Parasitology*, October 1960, **54**, 338). Further, 'the extreme simplicity of its administration, the absence of unpleasant side-effects, and the minimal interference with the patient's ordinary activities make dichlorophen the best available remedy for patients infected with *T. saginata*'. This conclusion is based upon his experience with 21 patients, most of whom were treated as outpatients: 19 were cured. The recommended dose for children is not less than 4 g. The practical advantage of dichlorophen, apart from its efficacy, is that there is no need to submit the patient to preliminary fasting or subsequent purging. The drug has a slightly laxative action and, if the requisite dose is taken before breakfast, two or three loose motions, containing the remains of the worm, will be passed during the next few hours. As it is seldom possible to find the scolex or anterior segments, the result of treatment cannot be known for three or four months. If by this time no further segments have been passed, cure can be assumed. No untoward reactions were noted in any of the patients.

The Burning Skin Syndrome

PRELIMINARY evidence that hydroxychloroquine may be of value in the symptomatic treatment of the 'burning skin syndrome' is presented by R. F. Butterworth (*Medical Journal of Australia*, September 17, 1960, **2**, 460), who reports the results in eight patients with this syndrome. In three it occurred in association with severe rheumatoid arthritis, in two following severe trauma to the hip-joints, and in three it occurred in old people. All of them 'appeared to be emotionally mature and faced their disabilities with courage and resolution'. All were completely relieved by hydroxychloroquine. The dosage was 600 mg. a day, divided into three equal doses. This was given for one month except in the patients with rheumatoid arthritis in whom the treatment was continued for three months. The mode of action of hydroxychloroquine in relieving this syndrome is not known.

Mesenteric Adenitis

THE chronic aspect of non-specific mesenteric adenitis is emphasized by J. B. L. Taylor

(*British Journal of Surgery*, September 1960, **48**, 178) in a review of 49 cases in children, aged 2 to 13 years. The main symptom is pain and its characteristic is that it is intermittent, colicky, or spasmodic. It comes on suddenly, lasts a few minutes, and settles quickly. It may be quite severe but between spasms the patient is fairly comfortable. The site of the pain may vary from time to time and may be difficult to localize. It is usually a mid-abdominal colic, but is sometimes in the right iliac fossa. Headache was present in 18 of the patients in this series. On examination there is always some abdominal tenderness in the right iliac fossa, or below and to the right of the umbilicus. The tenderness is not well localized and may vary in position at different examinations, but shifting tenderness has not been found to be a useful diagnostic sign. Abdominal rigidity is never present in the chronic cases, and only rarely in the acute episodes. In this series the children were never really ill and physical signs were not marked. In the differential diagnosis of the acute case, appendicitis is the important factor. Appendicitis also comes into the differential diagnosis of the chronic case, but equally important here are the periodic syndrome and abdominal migraine. In the 27 cases operated on in this series, the appendix was normal in 13, acutely inflamed in three, and chronically inflamed in 11. The essential point in treatment is to select the children who will benefit from appendicectomy. If there is no definite evidence of appendicitis, the author's practice is to treat these cases conservatively in the first instance. If, however, there is no improvement after a short period of conservative treatment and observation, operation is advised without delay.

Treatment of Acute Leprotic Neuritis

'A COMBINATION of "hyalase" and cortisone in lignocaine solution has a definite beneficial effect in acute leprotic neuritis', according to R. H. Thangaraj and Sarojini Thangaraj (*Leprosy Review*, October 1960, **31**, 295). This conclusion is based upon the findings in a series of 40 patients (38 lepromatous and two dimorphous), who had had one or two attacks previously. They were divided into four groups, each containing 10 patients. Three of these groups acted as controls, one receiving intraneural 'hyalase', another intraneural lignocaine, and the third a subcutaneous injection of distilled water over the affected nerve. The fourth group received 0.5 ml. of cortisone acetate (12.5 mg.) with 1000 units of 'hyalase' dissolved in 1 ml. of 1% lignocaine injected intraneurally. The injection was repeated four days later. In the patients with lateral popliteal neuritis the limb was immobilized with the knee in full extension and the foot in dorsiflexion. There was no immobilization in cases in which other nerves were involved. An assessment of the results shows that the best results were obtained in those patients receiving cortisone and 'hyalase'—eight obtaining 'complete relief' and one 'partial relief'. A follow-up eight months later confirmed the beneficial action of the cortisone-'hyalase' injection, only one patient having relapsed in this period.

Isolated Myocarditis and Sudden Death

THAT in London, excluding 'cot deaths' and poisonings, 'isolated myocarditis' is the cause of death in over 50% of cases of 'that bugbear of the forensic pathologist, the obscure autopsy', is the view advanced by Colin Corby (*Medicine, Science and the Law*, October 1960, **1**, 23). In support of his view he gives details of 32 of these 'obscure autopsies' which on histological examination proved to be examples of 'isolated myocarditis', which he defines as 'myocarditis of at present unknown etiology, occurring without endocarditis or pericarditis and without any pathological process to account for the myocardial inflammation'. The sex incidence was equal and, though the age-range was from 5 to 60 years, the cases fell predominantly into the young adult age-groups. In 28 cases death occurred suddenly (e.g. six collapsed in the street, two while playing football, five were found dead in bed, and two were found dead at home fully dressed). The previous history was not significant in any case. The incidence is approximately 0.35% of medico-legal necropsies carried out in the London area. In each case the diagnosis was made by histological examination of multiple sections of the heart. The predominant finding was an infiltration of inflammatory cells, mainly lymphocytes and monocytes with occasional polymorphs and eosinophils. Emphasis is laid upon the variation in the histological picture from area to area—some areas being completely normal. Although such cases seem to be rare it is suggested that there are probably many more which are missed because histological examination is not carried out on 'a normal-looking heart' or because inadequate sections are examined. The view is expressed that 'isolated myocarditis' appears to be 'a specific entity for which at present no cause can be found'.

REVIEWS OF BOOKS

Neoplastic Disease at Various Sites: Vol. III, *Cancer of the Rectum.* Edited by CUTHBERT E. DUKES, O.B.E., M.D., M.SC., F.R.C.S. Edinburgh and London: E. & S. Livingstone Ltd., 1960. Pp. 304. Illustrated. Price 50*s.*

CANCER of the rectum is one of the most important of contemporary problems in the civilized world. British surgeons lead in the treatment of the disease, and Cuthbert Dukes is the acknowledged leader and teacher of British proctology. On these grounds it is impossible to exaggerate the importance of this book. It deals with the subject in all its aspects, in some instances with a thoroughness and a wealth of detail that are beyond the needs and the comprehension of the average reader. Section I, for instance, contains three chapters by Dr. R. A. M. Case, of the Chester Beatty Institute, dealing with the figures of incidence and mortality with a completeness and in phraseology that no-one but a trained statistician could understand. With these possible exceptions every general surgeon, every postgraduate, and every candidate for higher surgical diplomas, must read the whole of this book carefully. In a symposium that is so good, the following chapters call for special comment: chapter X, an important section on 'Anatomical and physical considerations', by Alan Parks; chapter XI, a thoughtful paper on 'Diagnosis' by Edward Muir; chapter XII on 'Biopsy', by Gabriel, for its microphotographs. Chapter XIII by Goligher on the 'Choice of operation', as good a review as can be found anywhere; chapter XVII on 'Restorative operations', by Naunton Morgan; and chapter XXI on 'The Colostomy', by Ian Todd.

If any comment is justified, it might be suggested that in future editions a little more discussion on two clinical problems, the villous tumour of the rectum and lower colon, and the amœbomas, which seem to be limited to the cæcum and the rectum, and which are not necessarily preceded or accompanied by recognizable amœbic dysentery, would be appreciated.

Cancer: The Significance of Delay. By ROBERT SUTHERLAND, M.D., D.P.H. London: Butterworth & Co. (Publishers) Ltd., 1960. Pp. 213. Price 30*s.*

A GROUP of senior surgeons sat enjoying their coffee and cigars after the closing dinner of a convention of the International Society of Mastology. 'The trouble with cancer', said the Englishman, 'is that it is two diseases. The first can be cured by surgery, if early and radical enough; the second cannot be cured by any means yet available to us'. 'I agree', said the Swede, 'the first is the lymph-spreader, the second the blood-spreader'. 'It is not so simple', said the Scot, 'the first group inevitably passes into the second. It may do so secretly, undetected, within a few hours of the first change to malignancy in a single group of cells, or it may remain localized for twenty years, as it often does in the breast. When, why, and how does the change come about?'. 'That is the point', said the American; 'I do not want to know the cause of cancer, or rather I do not hope to know it; but I desperately want to know what keeps cancer in check, and I mean to find out'. Whilst this conversation reflects the outlook of the senior generation of surgeons today, the conviction is growing, particularly in the United States, that cancer is from the outset a systemic disease like measles or smallpox, and that cells will be found in the blood stream even in its early stages if the search is sufficiently thorough.

This book in spite of its title and the association of its author with the Yorkshire Council of the British Empire Cancer Campaign, is not a plea for cancer education, but a critical, comprehensive and carefully annotated review of all those factors—the tumour characteristics, the characteristics of the host, the environment, and the duration—that affect the progress of a cancer once it has appeared, and determine the prognosis. It is a really important book, and the surgeon who fails to read it will be doing himself an injustice.

The Treatment of Tropical Diseases. By W. H. JOPLING, M.R.C.P., M.R.C.P.ED., D.T.M. & H. Bristol: John Wright & Sons Ltd., 1960. Pp. 202. Price 20*s.*

SOME books are designed to be read through with pleasure, others, like a telephone directory or a railway time-table, to be referred to with advantage. This book is of the second category. Whosoever wishes to have accurate and up-to-date information on the chemotherapy of the majority of diseases conventionally called tropical can find it here. The most valuable parts of the book are those dealing with specific treatment, especially of the helminthic and protozoal infections. On the other hand, the remarks made under the heading of general treatment are largely, and perhaps inevitably, platitudinous. The discussion of the management of dehydration, which one would expect to find in connexion with cholera, appears instead in the article on bacillary dysentery and is somewhat lacking in clarity. For example, the author lists nine different solutions under the heading 'choice of parenteral fluid' but gives no precise

indication of their uses. Tropical sprue is dealt with sketchily from the dietetic viewpoint. Leprosy is well done, as might be expected. The work ends with a series of appendixes including one on the use of corticosteroids and one on antibiotics. The book should be useful to those preparing for the D.T.M. & H. and to practitioners in the tropics.

Clinical Pharmacology. By D. R. LAURENCE, M.D., M.R.C.P., and R. MOULTON, M.B. London: J. & A. Churchill Ltd., 1960. Pp. 490. Price 32*s*.

'THIS book is offered as a reasonably brief solution to the problem of combining practical clinical utility with some account of Pharmacology'. A welcome offering, indeed, which is generously fulfilled, and sure to be popular with students who have 'Applied Pharmacology and Therapeutics' in their final examination as is the case at present at Cambridge and London. Whether the text will be regarded as adequate for postgraduate reference is perhaps less certain but it is very readable, enlivened by a series of short quotations from original articles and eminent authorities, very up to date with several quotations from 1960 publications, and does not hesitate to condemn drugs as obsolete when there are newer and possibly more approved remedies, though sulphaguanidine still has a tremendous following in France and some support in Britain.

There are 29 chapters which cover the field both from the 'actions' and the 'uses' aspects and three appendixes—possibly additions after the book was complete: for the first, in addition to dealing with weights and measures and prescription writing, ends with an enchanting little essay on 'drug names' and could be an introductory chapter: the second, on 'dosage of antimalarial drugs', could be incorporated in chapter 4, and the third, on 'surgery in diabetic patients' could go in chapter 23. Less than justice is done to halothane, already accepted in the *B.P.* 1960 *Addendum*, and there are some odd variations on pharmacopœial dosage of barbiturates on p. 104 where the learner might suspect that quinalbarbitone and cyclobarbitone are more potent than the medium-acting group since 50-mg. doses are suggested. Incidentally, this table errs in giving 'medinal' as an equivalent for barbitone instead of for barbitone sodium. What is meant by tabulating, against mepyramine, 'a satisfactory drug as antihistamines go', or by inferring that this is effective in lower doses than promethazine or at least in sub-pharmacopœial doses? But these are trivial criticisms and it is to be hoped that the authors and their colleagues at University College Hospital will revise and continue to maintain a book which is fascinating as well as useful.

Edema: Mechanisms and Management. Edited by J. H. MOYER, M.D., and MORTON FUCHS, M.D. Philadelphia and London: W. B. Saunders Co., 1960. Pp. 833. Illustrated. Price £5 5*s*.

THIS volume embodies over 100 papers which were read at a symposium on salt and water retention held under the auspices of the Hahnemann Medical College in Philadelphia. At this meeting scientists representing different disciplines discussed in great detail the complex mechanisms underlying the production of œdema, and its relief by diuretic drugs. For good measure there are verbatim reports of a score of panel discussions at which points arising in the papers were elaborated or debated. In a preliminary section present-day views are presented on the intimate (electron-microscopic) anatomy of the kidney and on the functions of individual portions of the nephron (glomeruli, proximal and distal tubules and Henle's loop) including an exposition of the 'counter-current multiplier' concept of tubular function. These form a basis on which discussions of the body economy in respect of water and various electrolytes are founded and lead to discussion of the site and mode of action of diuretic drugs. The mercurials, carbonic anhydrase inhibitors, and thiazide groups are dealt with in detail. There follow sections on the problem of œdema in individual clinical syndromes—e.g. cardiac failure, renal disease, liver cirrhosis, toxæmia of pregnancy—and on the role of sodium retention and diuretic therapy in hypertension.

It is in no sense an easy book to read; in part this is due to some unavoidable repetition in individual contributions, but in greater measure it stems from the very complexity of the processes under discussion. It should prove on the one hand a valuable work of reference to those working in the field, and on the other, for postgraduate students and physicians, a convenient assembly of much of the newer knowledge of renal physiology and the derangements of function that occur in a wide variety of pathological states.

Hospital Infection: Causes and Prevention. By R. E. O. WILLIAMS, M.D., M.R.C.P., R. BLOWERS, M.D., L. P. GARROD, M.D., F.R.C.P., AND R. A. SHOOTER, M.D. London: Lloyd-Luke (Medical Books) Ltd., 1960. Pp. 307. Illustrated. Price 35*s*.

THE first half of this book describes the various forms of hospital infection. The sources of the

organisms and their behaviour in the community are summarized and an attempt is made to trace the probable pathways by which they travel. Infection caused by staphylococci is naturally dealt with at length, but adequate accounts are also given of gastro-intestinal, genito-urinary and the other forms of infection which may occur as a result of transfer of organisms from patient to patient while in hospital.

The second half describes the measures that can be taken to control such infection. Every detail of hospital routine is dealt with: the status and duties of the Control of Infection Officer; the design of wards and operating theatres; the techniques to be employed in them; the use of antibiotics; the design and operation of apparatus used for sterilization; and the employment of antiseptics together with recommendations as to the most suitable for each and every purpose. Written by four recognized authorities, the book is an admirable summary of present-day knowledge of a subject on which thousands of articles must have been written in the past decade. Many of them, being of doubtful value, have quite rightly been ignored and the authors have confined themselves to facts about which there is reasonable certainty. To have sifted so enormous a mass of information at all is in itself an achievement, but of equal merit is the way in which the facts are marshalled and presented. For there is a refreshing directness of approach, the writing is clear and lucid and there is an almost entire absence of statistics and similar hindrances to understanding.

Valuable as the first half of this book may be, it is the second half that will be especially welcome to the hospital pathologist. For here he will find how to answer the thousand and one questions he is asked from time to time. But it can also be recommended to surgeons, hospital administrators and nurses—in fact everyone who has to interest himself (or herself) in cross-infection. The only criticism that can be made is the inadequacy of the index, a serious lapse in a book that will almost certainly be used for reference as much as for reading.

Medical and Dental Aspects of Fluoridation. By W. A. CANNELL, M.R.C.S., L.R.C.P., D.P.H., L.D.S.R.C.S. London: H. K. Lewis and Co. Ltd., 1960. Pp. 125. Price 15*s*.

ONE wonders whether Sir James Crichton Browne, when addressing the British Dental Association in 1892 on the importance of a fluoride supply during the development of the teeth and the consequence of its deficiency in the production of inferior enamel, fully appreciated the great fund of literature and controversy that was likely to emanate from his prescient observation. It was an important part of Sir James' plea that the fluorine should be introduced via the pellicle of the wheat germ, protagonist as he was for whole-wheat bread. It is a long stride from that wholesome approach to fluoridation to the highly scientific review of the multiple aspects of the problem that Dr. Cannell produces. He is to be congratulated on the breadth of his study and the conscientious collection of references which are to be found at the end of each chapter of his work. The eleven chapters which comprise this text deal with the many aspects of the problem, including history, nutrition, physiology, public health works and finally a useful appendix on the increasingly important problem of fluoride compounds in industry. The book should attract a wide readership both in the medical and dental professions, and it is to be hoped that the intelligent layman will also give thought to the balanced appraisal of the question of artificial fluoridation of water, a subject on which there has been perhaps too much emotion and too little critical thought.

The Early History of Surgery. By W. J. BISHOP. London: Robert Hale Ltd., 1960. Pp. 192. Illustrated. Price 18*s*.

THIS is one of the most interesting books that could come into a surgeon's hands. There are many histories of surgery, of which one of the best known is the short account by Sir d'Arcy Power, but these, in presenting a continuous picture, tend to dwell on the highlights and the great personalities. The interest of this book is that the author writes of surgery as a whole, in many centuries and many countries, and gives a picture of a constant striving forwards, during which the disappointments and the setbacks are as interesting as the dramatic advances.

Such a review reminds us that many methods, since accepted as advances, were tried and failed centuries earlier. Blood transfusion was attempted repeatedly in the Middle Ages, and seems to have been occasionally successful. Appendicitis was known as a dangerous abdominal inflammation, and treated occasionally by drainage. Plastic surgery was advocated in India and Italy centuries before it was established on sound principles. Even antiseptic surgery was seen as an ideal by several men before Lister, and even he could not better the results obtained by his contemporaries, Spencer Wells and Lawson Tait, men who relied upon cleanliness and derided Lister's teaching.

The persistence for decades of methods that we now know to be not merely wrong but

harmful, such as bloodletting which persisted for centuries, and the washing out of the abdominal cavity with pints of antiseptic solutions that retarded the advance of the surgery of acute abdominal emergencies, reminds one that 'Knowledge comes, but wisdom lingers'. Altogether a most readable book.

NEW EDITIONS

The Practice of Medicine, edited by Sir John Richardson, M.V.O., M.D., F.R.C.P., in its second edition (J. & A. Churchill Ltd., 37*s.* 6*d.*) sets a commendable example by being about a hundred pages shorter than the first edition. This is but one example of the care that has been taken in the process of revision. Equally commendable is the improvement in the section on the alimentary tract. In view of the consistently high standard maintained by the fifteen contributors, there is little to criticize, but in the section on the cardiovascular system a disproportionate amount of space would seem to be given to the technicalities of cardiac catheterization and electrocardiography. Taken all in all, however, this is an excellent contribution to the subject for the undergraduate, with its emphasis on those clinical and practical aspects which form the basis of sound medical practice.

Clinical Psychiatry, by W. Mayer-Gross, M.D., F.R.C.P., Eliot Slater, M.D., F.R.C.P., D.P.M., and Martin Roth, M.D., F.R.C.P., D.P.M., in its second edition (Cassell & Co. Ltd., 63*s.*) retains the features that gave the first edition its characteristic flavour. Sections have been added on ecology, existentialism and Pavlovian concepts as applied to psychiatry, and the chapter on the epilepsies has been impressively rewritten. Articles on lysergic acid (L.S.D.), chlorpromazine and reserpine now appear in the chapter on pharmacology; and in other chapters there are brief references to the new anti-depressants, such as 'marsilid' (iproniazid) and 'tofranil' (imipramine). The Mental Health Act, 1959, is outlined only. Reference is made, however, to 'vocabulary reforms' (p. 600) showing a glimpse of the current legal classification. The book has grown by fifty pages. It retains its XVI plates, some of which, like parts of the chapter on administrative and legal psychiatry, are of historical interest rather than immediate practical value. It might be pruned without losing the qualities which have won for it a recognized place as a valuable work of reference.

Outline of Fractures, Including Joint Injuries, by John Crawford Adams, M.D., F.R.C.S., third edition (E. & S. Livingstone, 27*s.* 6*d.*).—The fact that a third edition of this work has been required so soon is good testimony to its excellence. It has been only very slightly enlarged. The importance of trauma in present-day life is well recognized and that general practitioners must play an important part in treatment, particularly in so-called minor injuries. The rehabilitation of injured patients depends upon efficient initial treatment and this book remains a most useful guide for all who see injuries early.

Essentials of Fluid Balance, edited by D. A. K. Black, M.D., F.R.C.P., second edition (Blackwell Scientific Publications, 20*s.*).—Since the first edition of this book was published three years ago, many other works on the same subject have been produced. Although some of the more recently published books have considerable merits, none surpasses Dr. Black's work in lucidity of exposition or literary elegance. The second edition differs from the first mainly in the insertion of more recent references to the ever-expanding literature of the subject, and to emendations which changes of emphasis or inference from recent research have made necessary. It seems unfortunate that the chapter on so-called 'acidosis' and 'alkalosis' should perpetuate the misconception that the changes encountered in these conditions are the result of primary alterations in the anions; until pathologists and clinicians grasp the central position of hydrogen-ion in disturbances of 'acid-base' metabolism much muddled thinking in this subject will continue. One also shares the regret, expressed in the preface, at the omission of a chapter on magnesium, but perhaps we may hope for an account of the metabolism of this ion in future editions. There is a bibliography of 349 references in which recent reviews are marked with an asterisk. For a short highly readable account of a difficult subject this is far and away the best available, and is recommended to everyone who is interested in the subject, whether their interest be primarily clinical or physiological.

The contents of the February issue, which will contain a symposium on 'The First Month of Life,' will be found on page A 138 at the end of the advertisement section.

Notes and Preparations see page 153.
Notes from the Continent see page 157.
Fifty Years Ago see page 159.
World Health News see page A 15.
Motoring Notes see page A 105.
Travel Notes see page A 109.
Bridge Notes see page A 113

NOTES AND PREPARATIONS

NEW PREPARATIONS

'ADCORTYL-A PARENTERAL' is an aqueous suspension of triamcinolone acetonide and is intended for 'intra-articular, intrasynovial, or intrabursal injection in the treatment of painful and inflammatory involvements of joints, and for intralesional (intradermal or sometimes subcutaneous) injection in the management of a variety of localized dermatological lesions'. Available in 5-ml. multidose vials containing 10 mg. in each ml. (E.R. Squibb & Sons Ltd., Edwards Lane, Speke, Liverpool 24.)

'DETIGON LINCTUS' contains 14 mg. of 1-o-chlorophenyl-3-dimethylamino-1-phenylpropan-1-ol and 80 mg. of potassium guaiacol sulphonate in each 4-ml. teaspoonful and is intended for the treatment of 'all kinds of cough'. It is said to be an expectorant and antitussive 'with dual action on the cough centre and a local effect in the throat'. Available in bottles of 4 fluid ounces (113 ml.). (FBA Pharmaceuticals Ltd., 37-41 Bedford Row, London, W.C.1.)

'FILON' tablets each contain 30 mg. of 3-methyl-2-phenylmorpholino-8-chlorotheophyllinate and 20 mg. of 2-(3-methyl-2-phenylmorpholino)-ethyl alphaphenylbutyrate hydrochloride. The preparation is described as 'a mild psychic energizer, antihypotonic and appetite depressant', and is said to be well tolerated. Available in containers of 100 tablets. (West Pharmaceutical Co. Ltd., 9 Palmeira Mansions, Church Road, Hove 3, Sussex.)

'S.7' preparations contain 1% bis-(2-hydroxy-5-chlorophenyl) sulphide which is described as 'a new non-toxic, non-irritant substance possessing powerful fungicidal and antibacterial properties against a wide range of pathogens associated with mycotic and bacterial infection of the skin'. Available as a jelly (tubes of 15 g.), as a cream (tubes of 30 g.), and as a powder (insufflators of 15 and 75 g.). (Calmic Ltd., Crewe, Cheshire.)

'SUSTACOL' (sustained action) tablets each contain 7.5 mg. of homatropine methylbromide and 72.5 mg. of phenobarbitone in a form allowing controlled release over a period of ten hours. They are intended for use as an antispasmodic in the treatment of spastic conditions of the gastro-intestinal tract 'including the irritable colon, mucous colitis and spastic constipation syndrome'. (Pharmax Ltd., Western House, Gravel Hill, Bexleyheath, Kent.)

'TRANSID' tablets each contain 0.3 g. of polyaminostyrene and are intended for the treatment of gastric hyperacidity in peptic ulcer and 'various forms of dyspepsia'. The preparation is said to be free of the disadvantages associated with many other antacids as it 'does not interfere with digestion and causes neither constipation nor diarrhœa'. Available in cartons of 100 foil-packed compressed tablets. (Duncan, Flockhart & Co. Ltd., 16 Wheatfield Road, Edinburgh 11.)

'URELIM' tablets (formerly known as 'longacid') each contain 0.5 g. of *p*-carboxybenzenesulphondiethylamide and are intended primarily for the long-term treatment of gout but 'may also be indicated when hyperuricæmia is found in association with musculo-skeletal disorders or certain systemic diseases'. Available in containers of 100 and 500 scored tablets. (Ward, Blenkinsop & Co. Ltd., Fulton House, Empire Way, Wembley, Middlesex.)

PHARMACEUTICAL NOTES

ARMOUR PHARMACEUTICAL CO. LTD. announce that their chymotrypsin preparation 'chymar' is now available in a new form, known as 'chymar aqueous', supplied in vials of 5 ml., each millilitre containing 5000 Armour units. (Hampden Park, Eastbourne, Sussex.)

CAMDEN CHEMICAL CO. LTD. announce that their orphenadrine hydrochloride preparation 'disipal' is now available in packs of 1000 and 10,000 as well as 100 and 250. (61 Gray's Inn Road, London, W.C.1.)

WARD, BLENKINSOP & CO. LTD. announce that 'penotrane' pessaries are now available in an additional strength, to be known as 'strong penotrane pessaries', each 4-g. pessary containing 5 mg. of phenylmercuric dinaphthylmethane disulphonate. (Fulton House, Empire Way, Wembley, Middlesex.)

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be held on Wednesday, January 18, at 8.15 p.m., when the subject for discussion will be 'Vertigo'. The opening speakers will be Dr. J. A. Currie, Mr. C. Gill Carey, and Dr. Denis Williams.

FORTHCOMING CONFERENCE

THE *Third World Congress of the International Federation of Gynæcology and Obstetrics* will be held in Vienna from September 3 to 9, 1961. Full details may be obtained from the Scientific

Secretary of the Congress at Alserstrasse 4, Vienna 9, Austria.

FILM NEWS

THE *Fourth International Festival of Medical and Scientific Films* will be held in Turin from June 3 to 15, 1961, under the auspices of *Minerva Medica*. Films must be submitted by May 15, 1961. Full details may be obtained from the Secretariat of the Festival, *Minerva Medica*, Corso Bramante 83-85, Turin, Italy.

NEW JOURNAL

Medicine, Science and the Law is the official journal of the British Academy of Forensic Sciences and 'will devote its pages to presenting articles and features addressed to all, whether members of the academy or not, whether specialists or amateurs, in the fields of Medicine, Science and the Law'. The journal, the first issue of which is dated October 1960, will be published quarterly and the annual subscription is 63*s*. (U.S.A. $10). The editor is Dr. Francis Camps and the publishers are Sweet & Maxwell Ltd., 11 New Fetter Lane, London, E.C.4.

THE WOLFSON FOUNDATION

THE report of the first five years (1955-60) of the Wolfson Foundation, the medical trustees of which are Sir Stanford Cade and Lord Evans, shows that the grants made in this period totalled £3.3 million. Of this sum, 1¼ million are classified under 'health' and 1¾ million under 'education'. The largest individual grant in the 'health' section was £450,000 to the Royal College of Physicians.

TUBERCULOSIS AND RE-EMPLOYMENT

THE report by the Joint Tuberculosis Council on 'Tuberculosis: Report on the Reception of Ex-Patients in Respect of Re-Employment and Superannuation, Life Assurance and Emigration', which was published in *Tubercle* (October 1960, 41, 370), provides a review of the subject which will prove of interest and value to many general practitioners. As it points out, the introduction of chemotherapy has revolutionized the outlook in tuberculosis but, unfortunately, employers and life assurance companies are not altering their outlook as quickly as they might. The result is that many recovered tuberculosis patients are finding it increasingly difficult to obtain suitable employment or adequate life assurance coverage.

U.S. DRUG RESEARCH

THE United States pharmaceutical industry spent a record $197 million last year on research, according to the Pharmaceutical Manufacturers' Association. This was 16% higher than in 1958. More than $18 million of the total were spent outside the industry in the form of grants to medical schools and hospitals. An estimated 100,200 chemicals, compounds and other substances were investigated in the industry's search for new drugs. Of these, 36,000 were in the field of cancer chemotherapy, and 28,200 in the field of allergic and infectious diseases. The estimated record and development expenditure for 1960 is $214 million.

FOOD HYGIENE

'THE conditions under which food is prepared and marketed in this country are, generally speaking, as good or better than those of any other. This is reflected by the very small number of complaints received from the public and the falling-off since the war years of the amount of food condemned by the inspectors. In all matters relating to food handling and food hygiene the personal factor is of major importance. Facilities provided will be used infrequently by the unsatisfactory type of person whereas the person of clean habits will maintain a good standard without the necessity of constant supervision'.—The Group Food Inspector for Lewisham, in the annual report of the Medical Officer of Health for 1959.

HEALTH VISITORS

'How much routine visiting of the healthy infant is really necessary now that the maternity and child welfare services are known and accepted and now that the general practitioners are taking an increasing interest in the normal development of the children under their care Is it not now time to take stock of the position, and having seen with satisfaction the great improvement in the general health of mothers and children, the low maternal and infant mortality (for which much of the credit must go to the tireless energy and enthusiasm of the health visitors) conclude that the time has come for further efforts in different fields '—Annual Report of Dr. J. Adrian Gillet, the Medical Officer of Health of Dagenham for 1959.

'LOVE AND MARRIAGE'

'DURING the year requests were again received from youth clubs for me to lecture on the subject of "Love and Marriage". Perhaps the most frightening experience which a health education officer may meet in the very varied work which he ought to perform is to drive up to a youth club; to venture inside; to see between 100 and 200 young people jiving desperately away to a cacophony of sound which is almost ear splitting as it cascades over the floor; to cast an eye round the young people and note that perhaps

a third of them are in teddy boy or girl clothing and to think that in two minutes' time this seething mass of young people must be reduced to a quiet group willing to listen to what is to be said upon a most important and delicate subject. There is no doubt, however, to judge by the attitude of club members and by letters received afterwards, that these lectures do fill a long felt need and additional requests from surrounding clubs are frequently received'.—The Health Education Officer in the Annual Report of the Principal School Medical Officer of Middlesex for 1959.

U.S. SPORTS FATALITIES

A REPORT published by the American Football Coaches' Association, covering the five years, 1955-59, shows that during this period football was responsible for 108 deaths in the United States, 81 of which were directly due to injuries. The remaining 27 deaths were caused by heat stroke, heart failure or other conditions. In the same period, boxing was responsible for 18 deaths—12 amongst amateur boxers and six among professionals. Attention is drawn to the fact that there has been an increase in the number of deaths amongst amateurs, five of the 12 fatalities occurring during 1959 alone.

GLYCYRRHETINIC ACID AND LEUKÆMIA

'A FURTHER parallel between the activity of adrenal cortical hormones and glycyrrhetinic acid' is reported by W. Logemann *et al.* (*Nature* (*Lond.*), 1960, **187**, 607). This consists of a retarding effect on a transplantable myeloma in rats. This effect was obtained with both α- and β-glycyrrhetinic acid, but the α- compound appeared to be more active. No such action was obtained with other tumours including a mouse sarcoma.

CIGARETTES, EMOTION AND TUBERCULOSIS

D. M. KISSEN, who has previously reported that certain emotional factors—usually 'a break or threatened break with a loved person'—were a significant cause of relapse in pulmonary tuberculosis, has now investigated the relationship between emotional factors, smoking and relapse in pulmonary tuberculosis (*Hlth Bull.* (*Edinb.*), 1960, **18**, 38). He found no association between cigarette smoking and relapse, but a 'suggestive association' between the incidence of cigarette smoking and the incidence of specific emotional factors preceding the onset of the illness. Further, patients with emotional factors who were cigarette smokers showed a 'suggestively lesser tendency' to relapse than such patients who were non-smokers.

As a result he suggests that: (a) 'The statistical association between cigarette smoking and tuberculosis must be considered in the light of the association between smoking and emotional factors in tuberculosis before attributing an etiological role to smoking'. (b) 'Those with emotional factors after recovery and who are cigarette smokers may be less likely to relapse than those with emotional factors who do not smoke'.

AN OBSTETRICAL CURIOSITY

AN obstetrical curiosity, in the form of a patient with twins, with an interval of sixty-five days between the birth of the two infants, is reported by P. Drucker and his colleagues (*Amer. J. Obstet. Gynec.*, 1960, **80**, 761). The patient was a 37-year-old, gravida IV, para III Negro woman, whose expected date of confinement was March 5, 1959. On September 25, 1958, she gave birth to a live infant, weighing 375 grammes, who died fifteen minutes after birth. On admission to hospital she was found to have a retained placenta and intra-uterine infection. Before the presence of a second viable fœtus was diagnosed, she was given an infusion of pitocin. On December 2, 1958 (i.e. sixty-five days after the birth of the first twin), she gave birth to a viable infant, weighing 1,390 grammes. Six months after the birth of the second twin, hysterography revealed a small contracted uterine cavity with no congenital defects.

PUBLICATIONS

Essentials of Chemical Pathology, by D. N. Baron, M.D.—When this book was first published, our reviewer (*The Practitioner*, 1958, **180**, 265) described it as 'remarkably complete' and 'invaluable not only to the specialist in the subject but also as a reference book for all practitioners'. A paper-cover edition is now available (price 10*s.* 6*d.*) in addition to the cloth-bound edition (price 25*s.*). (English Universities Press, Ltd.)

Equipment for the Disabled.—This publication consists of four loose-leaf volumes which constitute a catalogue of aids for the disabled, and as such it attempts to fulfil a need. Those who have practical experience in dealing with the problems of the handicapped will be able to judge the usefulness of the ideas illustrated. Others, however, unless they possess the requisite intuition and insight may well be confused by the vast variety confronting them and will be in danger of prescribing gadgets which are of little or no practical value. Certain items listed are in normal supply, free of charge, through the Ministry of Health, e.g. wheel-chairs. One is constantly surprised, however, by the number of people who do not realize this, and the

fact that these chairs are listed with their price would seem to lend support to this fallacy.

In spite of the comprehensiveness of these volumes, one is surprised to notice the omission of certain fairly well-known and useful ideas of equipment which are of proven value; and it is also difficult to understand the point in attaching names of hospitals to most of the illustrations when no mention whatsoever is made of a well-known London teaching hospital which has done most of the important pioneer work on this subject, and whose ideas have been freely drawn upon throughout this country and abroad. (Polio Research Fund, price £6.)

Casualty Services and their Setting is the report of a survey carried out by a steering committee appointed by the Nuffield Provincial Hospitals Trust. The survey covered 20 casualty departments serving over 5 million people, and the conclusion reached is that 'there is a need for leadership and urgent executive action on the part of hospital authorities to review, reorganize and improve the service for casualties.' Among the many points stressed is the need for the 'fullest consultation' as to 'how general practitioners can help to relieve hospitals of their burden of providing care for the relatively minor, non-urgent conditions'. (Oxford University Press, price 7*s.* 6*d.*)

Report of the 1960 *Conference on the Care of the Deaf* contains the papers read and details of the discussions held at the conference organized by the National Institute for the Deaf in London last October. (National Institute for the Deaf, price 8*s.*)

Socrates on the Health Service: Dialogues of Today is a collection of twenty-four articles which originally appeared in the *Lancet*. (*Lancet*, price 5*s.*)

The Hospital Gazetteer 1960 provides details of the accommodation, staff and amenities at hospitals in the United Kingdom. It will prove most valuable to all doctors seeking junior hospital appointments. A series of abbreviations allows an amazing amount of information to be packed into a commendably small space. (British Medical Association, price 5*s.*)

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the Year 1959. *Part II: On the State of the Public Health.*—One of the interesting sections in this, the annual report of the chief medical officer to the Ministry, is that devoted to 'Food and nutrition'. It draws attention, for instance, to three cases of tuberculous adenitis in a school, in which the source of infection was tracked down to the Friesian tuberculin-tested herd from which the school obtained its milk supply. It also discusses what has come to be known as the broiler industry. 'Reliable sources', it is said, 'give the sales figures for 1959 as exceeding 75 million birds, with estimates of future expansion to twice that figure in the next three or four years'.

A third problem dealt with is that of antibiotics in milk. Attention is drawn to the fact that a survey has shown that penicillin could be detected in 3% to 4% of milk samples in this country, and that this originated from use in the treatment of bovine mastitis. It is noted that 'even the small concentrations of penicillin found in samples of bulked milk' are sufficient to produce allergic reactions in penicillin-sensitive patients. The Milk Marketing Board have now introduced into their contracts with farmers a clause which prohibits the sale to the Board of milk from cows undergoing treatment with antibiotics within forty-eight hours of the last treatment. (H.M. Stationery Office, price 13*s.*)

Radiological Hazards to Patients.—The second report of the committee appointed, under the chairmanship of Lord Adrian, to investigate this problem, is devoted to the genetic dose: i.e. the genetic risk to future generations. On the whole, it presents a reassuring picture, as it finds that the total annual genetic dose from diagnostic radiology is 14.1 millirœntgens (mr) per person. Even when the annual genetic dose from radiotherapy (5.2 mr) is added, the final total of 19.3 mr per person per year is less than that attributed to diagnostic radiology alone (22 mr) by the Medical Research Council in 1956. It is pointed out, however, that the position could be much improved without in any way depriving patients of essential x-rays, and recommendations are put forward which would reduce the total annual genetic dose to 6 mr or less. (H.M. Stationery Office, price 6*s.*)

Our Children's Teeth is the interim report of the committee appointed last year by the Secretary of State for Scotland 'to examine in all their aspects the measures necessary to secure public awareness in dental matters, to advise on the form that publicity should take, and to ensure that the several agencies carrying it out work together'. The picture it presents is as depressing as that in other parts of the United Kingdom: e.g. in 1958, 3,609 children in Scotland, aged up to 16, had whole or partial dentures fitted under the National Health Service. (H.M. Stationery Office, price 1*s.* 6*d.*)

NOTES FROM THE CONTINENT

A European Newsletter

BELGIUM

Salicylate therapy.—Detailed pharmacological and clinical findings purporting to support the thesis that sodium salicylate and acetylsalicylic acid act by stimulating the hypothalamus, the anterior lobe of the pituitary and the suprarenal cortex, is adduced by Professor Roskam and Dr. van Cauwenberghe, of the University of Liège, in a paper read recently before the Royal Belgian Academy of Medicine. Their experiments in rats indicated a striking parallelism between the effects obtained when the blood salicylate level reached 35 mg.% and those obtained following the injection of corticotrophin. Their clinical findings correlated with the experimental findings. As a result of this investigation, it is recommended that the initial treatment of acute rheumatic fever should be with cortisone, and that this should gradually be replaced by salicylates. The advantage of this technique, it is claimed, is that it avoids any risk of diminishing the activity of the suprarenal cortex, and the results are said to be generally satisfactory.

Eosinophil granuloma.—According to L. Jeanmart-Michez, of the radiodiagnostic department of St. Peter's Hospital, Brussels, eosinophil granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophil granulomatosis are all manifestations of one underlying pathological process—a disturbance of the reticulo-endothelial system. He gives details of three cases of eosinophil granuloma, all of which were cured by radiotherapy with or without surgical curettage. On the other hand, two cases (aged 2¼ and 2½ years respectively) of Letterer-Siwe disease, of which details are also given, both died in spite of surgical, radiotherapeutic and medical treatment.

Disc necrosis following aortography.—Attention is drawn by M. Demoulin to what is described as a largely unknown complication of aortography: namely necrosis of an intervertebral disc and the two apposing vertebral bodies. He has encountered four such cases using a tri-iodide contrast medium, but has not yet encountered a case using a di-iodide medium. The presenting clinical features are pyrexia and pain, starting immediately after aortography and persisting for around six months; at least, the pain usually persists for this period, but the temperature settles sooner. The radiological changes first occur two to three months later, and are characterized by nipping of the disc, destruction of the cortex of the two neighbouring vertebral bodies, and an osteogenic reaction with the formation of osteophytes.

A new digitalis glucoside.—Details are given by R. Loraux and A. Charlier, of St. Peter's Hospital, Louvain, of a clinical trial in 50 patients of a new pentaglucoside extract of digitalis. These show that the new extract has a 'spectacular' effect in slowing the pulse rate in atrial fibrillation and is equally effective in converting atrial flutter into atrial fibrillation. Apart from nausea, which occurred in six patients, all of whom were either elderly or had previously been receiving digitalis, side-effects occurred in six patients: two cases of coupled rhythm, and four of atrio-ventricular block. These arrhythmias were all the result of overdosage and cleared promptly on withdrawal of the drug and the administration of potassium chloride or ephedrine. The view is expressed that this new extract has a wider margin of therapeutic safety than other digitalis preparations.

Arterial prostheses.—According to J. van der Stricht, of the department of vascular surgery, St. Peter's Hospital, Brussels, although a segmental obliteration of an artery, demonstrated radiologically, is a *sine qua non* for operation, this by itself is not sufficient. In addition, there must be an assessment of the functional state of the arterial tree behind the block. No surgical treatment can be successful unless there is a fair degree of correlation between the 'inflow' and the 'outflow' of the graft or resected portion of the artery. Speaking generally, thrombo-endartectomy is the treatment of choice when only a short segment of artery is involved. When a longer section is involved, an arterial graft or an artificial arterial prosthesis is preferable. It is pointed out that the introduction of arterial grafting has not excluded the use of lumbar sympathectomy in selected cases.

GERMANY

Liver disease.—This was the theme of the congress on metabolism held recently in Bad Mergentheim. In his introductory address, Professor Kalk, of Kassel, discussed the social significance of liver diseases. He criticized severely the failure of the Federal Republic to make hepatitis a notifiable disease, and drew attention to the fact that such notification is compulsory in East Germany. He attributed the marked increase of chronic liver disease to previous epidemics of hepatitis. It has been estimated that 5 million cases of hepatitis occurred during the last War.

The following are some of the points brought out during the congress. A large number of cases of epidemic hepatitis—some say as many as 20%—run an anicteric course. In 1956, the number of cases of epidemic hepatitis in Federal Germany was estimated to be 114,000, and this figure does not include the anicteric cases. One speaker estimated that at the present day there are 1 million people with liver disease in Federal Germany.

In spite of the advances that have been achieved in laboratory diagnosis, including liver biopsy, emphasis was laid upon the persisting importance of a careful clinical examination. As one speaker put it, an enlarged hard liver is a diseased liver even though the laboratory tests be normal. There is a real danger these days of the doctor developing a 'laboratory psychosis', the chief manifestation of which is over-dependence on laboratory reports.

Although the prognosis in hepatic coma is much better today than it was a few years ago, stress was laid upon the importance of careful differentiation of the various forms of coma. In the discussion on treatment of liver disease, a warning was issued against premature promises of cure—particularly when the disease process is still active, and emphasis was laid upon the necessity for all cases of hepatitis being treated in hospital.

Liver disease and gastric resection.—Liver disease was also the main topic of discussion at a conference devoted to digestion and enzymes. One speaker drew attention to the frequency of liver changes in patients who had had gastric resection. Of 214 cases of resection of the stomach, 20% showed changes in material obtained from the liver by biopsy, and another 42% showed definite abnormalities in liver-function tests.

Enzyme tests of liver function.—In a review of enzyme tests of liver function, the view was expressed that the serum-glutamate-pyruvate-transaminase test (the S.G.P.T. test) is the most sensitive. The strongest positive reaction with this test is obtained in acute virus hepatitis at the beginning of the illness. Quite often a positive result may be obtained weeks before the clinical onset of the illness. During the course of the infection a lowering of the transaminase level often precedes a fall in the serum bilirubin. On the other hand, a secondary rise in the transaminase level is an indication of a threatened relapse.

In chronic liver disease the transaminase level may be normal or even reduced, whereas in toxic hepatitis it is always raised. The greatest value of the enzyme tests is in differential diagnosis. In cases of obstructive jaundice, in which the obstruction is not of long standing, and there has therefore been little liver damage, the transaminase level is only slightly raised. It is a sign of the times that at this conference, as at the conference on metabolism, it was found necessary to issue a warning against overvaluing the significance of these tests. As one speaker expressed it, in his enthusiasm over these tests, the doctor must not forget the patient and his liver!

The problem of epilepsy.—At the twelfth German conference on therapeutics a session was devoted to the problem of epilepsy. One speaker drew attention to the increasing age of 'invalidism' of epileptics. This has relatively little to do with advances in therapy, but (at least in Germany) is attributable almost entirely to the shortage of manpower resulting from the tremendous economic expansion during recent years. As a consequence, many more epileptics are in employment than would normally be the case. It is interesting to note the emphasis that was laid upon hypoglycæmia in the differential diagnosis of epilepsy, but perhaps the most interesting paper was that of Mikorey, who propounded the theory that the treatment of grand mal may lead to what he described as a 'splintering' into attacks of petit mal which may be more difficult to influence therapeutically. As petit mal is not necessarily the lesser of the two evils, he questioned the wisdom of aiming at complete freedom from attacks of grand mal, and advised that anticonvulsant therapy should be used with the utmost caution and with careful attention to the details of each individual case.

'Notes from the Continent' are produced in collaboration with the Editors of *Bruxelles-Médical* (Belgium), *Le Concours Médical* (France), *Münchener Medizinische Wochenschrift* (Germany), and *Minerva Medica* (Italy).

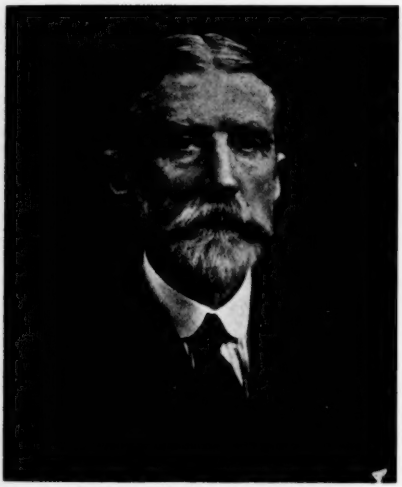
THE PRACTITIONER

Fifty Years Ago

'Nobody feels for my poor nerves'.—Jane Austen: *Pride and Prejudice.*

JANUARY 1911

THE importance of distinguishing between neurasthenia and the conditions associated with 'grave organic or constitutional disease which simulate it' is stressed by F. W. Mott, M.D., F.R.S., F.R.C.P., Physician to Charing Cross Hospital; Pathologist to the London County Asylums, in his article on 'Neurasthenia and some associated conditions'. After enumerating



Diarmid Noël Paton, M.D., F.R.C.P.Ed., F.R.S., LL.D. (1859-1928)

these conditions he suggests how a correct diagnosis may be made. Distinguishing between the melancholic and the neurasthenic he writes: 'The melancholic patient presents general subjective symptoms of depression, sadness, insomnia, and disgust with everything, and he is preoccupied with his state of health. . . . The neurasthenic complains of his sufferings and may have groundless fears of grave disease without sufficient reason, but there the similarity ends'.

In 'Neurasthenia and drugs' David Ferrier, M.D., F.R.S., Consulting Physician to the National Hospital for the Paralysed and Epileptic, Queen's Square, and to King's College Hospital, points out that with the typical neurasthenic 'his sense of fatigue and prostration is altogether disproportionate to its cause'. He warns against being led into treating individual symptoms, 'bromides, strychnine, phosphorus and its compounds, *et hoc genus omne*; high frequency, vibrations, hydropathy, stomach washings, intestinal irrigations, etc. These things, good in themselves in suitable cases, are in the neurasthenic often distinctly injurious, and tend to foster in his mind the belief that he is physically ill'. In his closing paragraph he mentions the desirability of getting patients back to their usual occupations: 'I am in the habit of telling my patients who find the regime a hard one that it is better to be ill at work than ill in idleness'.

Dealing with 'Traumatic neurasthenia', Wilfred Harris, M.D., F.R.C.P., Physician to St. Mary's Hospital, and to the Hospital for Epilepsy and Paralysis, Maida Vale, says the symptoms do not differ from those of neurasthenia due to other causes. 'Phobias may develop, especially in relation to circumstances connected with the accident, thus an unreasoning dread of horses, a railway train, a crowd, etc., may obsess a person whose injury was acquired through one of these causes'. In discussing treatment he writes: 'Moral encouragement from the attending physician is a great factor in early recovery'.

Ernest Clarke, M.D., B.S., F.R.C.S., Surgeon to the Central London Ophthalmic Hospital; Consulting Ophthalmic Surgeon to the Miller General Hospital, contributes an article on 'Neurasthenia and eyestrain'. He alludes to the 'nervous breakdowns' of Carlyle, Darwin, and Huxley which were attributable to eyestrain. 'We must remember', he writes, 'that neurasthenia and eyestrain are rarely seen in uncultured classes. Dairymaids and barmaids do not suffer, but the 'highly strung' neurotic lady of Belgravia is marked out as a likely victim'. He concludes: 'When the simple life was the rule, peripheral irritation and nerve waste, such as eyestrain produces, made little or no impression on the individual, but who can doubt its bad effect in this twentieth century of turmoil and worry'.

In his article on 'Neurasthenia and gastralgia' Robert A. Fleming, M.D., F.R.C.P., Assistant Physician, Royal Infirmary, Edinburgh, says of prognosis, this 'is largely one of neurasthenia itself. Remove the cause and the associated gastric pain and disturbance will gradually dis-

appear'. Clive Riviere, M.D., F.R.C.P., Physician, East London Hospital for Children, writes on 'Neurasthenia in children'. 'The treatment of the neurasthenic boy or girl', he says, 'resolves itself into the removal of the cause, whether over-pressure or want of sleep, or both'.

Discussing 'The sexual element in the neurasthenia of men', Gordon Holmes, M.D., M.R.C.P., Assistant Physician to the National Hospital for the Paralysed and Epileptic, and to the Seamen's Hospital, Greenwich, expresses the opinion that 'it seems possible to conclude that though the sexual element may be an indirect causal factor in the pathogenesis of neurasthenia . . . sexual abuses and troubles can rarely excite the disease directly'.

In 'Neurasthenia and diet' D. Noël Paton, M.D., C.M., F.R.C.P.Ed., Regius Professor of Physiology, Glasgow University, states that 'in dealing with the hypersensitive neurasthenic everything should be done to secure that the digestive processes are uninterrupted by psychic disturbances, and that the environment at meal times should, as far as possible, remove the worries and troubles which so persistently beset him'. He advises the practitioner 'in the present state of our ignorance of . . . neurasthenia on the one hand, and of the normal course of the intimate metabolism of food-stuffs on the other' to recommend a diet deemed suitable for the individual patient. He concludes by saying: 'It is needless to deal seriatim with the dietary management of all the many conditions which are either primarily or secondarily connected with the neurasthenic state. To do so would be to treat of the diet of every morbid condition to which flesh is heir'.

Born and educated in Edinburgh, Diarmid Noël Paton graduated M.B., C.M. with first-class honours in 1882, and was awarded a gold medal for his M.D. thesis in 1885. He held house appointments at the Royal Infirmary, Edinburgh, and at the Royal Hospital for Sick Children. Appointed director of the research laboratory of the Royal College of Physicians of Edinburgh in 1889, he became professor of physiology at Glasgow University in 1906. Elected F.R.S. in 1914, he served on the Medical Research Council from 1918 to 1923. He received an honorary LL.D. from his old University in 1919. Paton constantly revised his courses and provided his students with fresh and stimulating fare. His researches included studies on urea, the thyroid, respiration, and poverty, nutrition, and growth. Tall and handsome, he had much of the artistic temperament of his father, the distinguished artist, Sir Joseph Noël Paton.

'Notes from Foreign Journals' quotes from an article by Rockwell: 'Neurasthenia is no imaginary disease, and no appeal to the imagination alone will overcome the profound loss of nerve tone, or rearrange the delicate fibrillary connection of the neurons'.

T. H. B.

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